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| <p>(51) International Patent Classification ⁷ : C07K 14/00</p> | <p>A2</p> | <p>(11) International Publication Number: WO 00/26245</p> <p>(43) International Publication Date: 11 May 2000 (11.05.00)</p> | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| <table style="width: 100%;"> <tr> <td style="width: 50%; vertical-align: top;"> <p>(21) International Application Number: PCT/US99/26048</p> <p>(22) International Filing Date: 4 November 1999 (04.11.99)</p> <p>(30) Priority Data:</p> <table style="width: 100%;"> <tr> <td style="width: 60%;">60/172,255</td> <td style="width: 20%;">4 November 1998 (04.11.98)</td> <td style="width: 20%;">US</td> </tr> <tr> <td>60/172,252</td> <td>24 November 1998 (24.11.98)</td> <td>US</td> </tr> <tr> <td>60/172,214</td> <td>22 December 1998 (22.12.98)</td> <td>US</td> </tr> <tr> <td>60/121,896</td> <td>26 February 1999 (26.02.99)</td> <td>US</td> </tr> </table> <p>(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Applications</p> <table style="width: 100%;"> <tr> <td style="width: 60%;">US</td> <td style="width: 20%;">60/172,255 (CIP)</td> <td style="width: 20%;">Filed on 4 November 1998 (04.11.98)</td> </tr> <tr> <td>US</td> <td>60/172,252 (CIP)</td> <td>Filed on 24 November 1998 (24.11.98)</td> </tr> <tr> <td>US</td> <td>60/172,214 (CIP)</td> <td>Filed on 22 December 1998 (22.12.98)</td> </tr> <tr> <td>US</td> <td>60/121,896 (CIP)</td> <td>Filed on 26 February 1999 (26.02.99)</td> </tr> </table> <p>(71) Applicant (for all designated States except US): INCYTE PHARMACEUTICALS, INC. 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| <p>(57) Abstract</p> <p>The invention provides human membrane transport proteins (MTRP) and polynucleotides which identify and encode MTRP. The invention also provides expression vectors, host cells, antibodies, agonists, and antagonists. The invention also provides methods for diagnosing, treating, or preventing disorders associated with expression of MTRP.</p> | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |

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MEMBRANE TRANSPORT PROTEINS

TECHNICAL FIELD

This invention relates to nucleic acid and amino acid sequences of membrane transport
5 proteins and to the use of these sequences in the diagnosis, treatment, and prevention of membrane
transport disorders; immune/inflammatory disorders; and cell proliferative disorders including cancer.

BACKGROUND OF THE INVENTION

Eukaryotic cells are bound by a lipid bilayer membrane and subdivided into functionally
10 distinct, membrane bound compartments. The membranes maintain essential differences between the
cytosol, the extracellular environment, and the contents of intracellular organelles such as the Golgi or
the endoplasmic reticulum. As lipid membranes are highly impermeable to most polar molecules,
transport of essential nutrients; metal ions such as K^+ , NH_4^+ , P_i , SO_4^{2-} ; sugars; vitamins; metabolic
waste products; cell signaling molecules; drugs; peptides; and proteins and other macromolecules
15 across lipid membranes and between organelles must be mediated by a variety of transport molecules.
Many transport mechanisms are substrate specific, with each transport protein carrying particular
members of a molecular class, such as ions, sugars, or amino acids, across membranes. For example,
amino acids are imported into cells via specific amino acid permeases.

Transport proteins are multi-pass transmembrane proteins, which either actively transport
20 molecules across the membrane or passively allow them to cross. Active transport involves
directional pumping of a solute across the membrane, usually against an electrochemical gradient.
Active transport is tightly coupled to a source of metabolic energy, such as ATP hydrolysis or an
electrochemically favorable ion gradient. Passive transport involves the movement of a solute down
its electrochemical gradient. Transport proteins can be further classified as either carrier proteins or
25 channel proteins. Carrier proteins, which can function in active or passive transport, bind to a specific
solute to be transported and undergo a conformational change which transfers the bound solute across
the membrane. Channel proteins, which only function in passive transport, form hydrophilic pores
across the membrane. When the pores open, specific solutes, such as inorganic ions, pass through the
membrane and down the electrochemical gradient of the solute.

30 Transport proteins play roles in antibiotic resistance, toxin secretion, ion balance, synaptic
neurotransmission, kidney function, intestinal absorption, tumor growth, and other diverse cell
functions (Griffith, J. and C. Sansom (1998) The Transporter Facts Book, Academic Press, San Diego
CA, pp. 3-29). A variety of human inherited diseases are caused by mutation of transport proteins.
For example, cystinuria is an inherited disease that results from the inability to transport cystine, the

disulfide-linked dimer of cysteine, from the urine into the blood. Accumulation of cystine in the urine leads to the formation of cystine stones in the kidneys. Also, many transport proteins are composed of subunits that may confer specificity for the tissue in which the transport mechanism functions, and are therefore associated with tissue-specific disorders. Examples of transport proteins include

5 facilitative transporters, the secondary active symporters and antiporters driven by ion gradients, and active ATP binding cassette transporters involved in multiple-drug resistance and targeting of antigenic peptides to MHC Class I molecules, and the E1-E2 cation transport ATPases.

Carrier proteins which transport a single solute from one side of the membrane to the other are called uniporters. In contrast, coupled transporters link the transfer of one solute with

10 simultaneous or sequential transfer of a second solute, either in the same direction (symport) or in the opposite direction (antiport). For example, intestinal and kidney epithelium contains a variety of symporter systems wherein the movement of sodium into the cell down its electrochemical gradient co-transport a second solute into the cell. The sodium gradient that provides the driving force for solute uptake is maintained by the ubiquitous Na^+/K^+ ATPase. Sodium-coupled transporters include

15 the mammalian glucose transporter (SGLT1), iodide transporter (NIS), and multivitamin transporter (SMVT). These three transporters have twelve putative transmembrane segments, extracellular glycosylation sites, and cytoplasmically-oriented N- and C-termini. NIS plays a crucial role in the evaluation, diagnosis, and treatment of various thyroid pathologies because it is the molecular basis for radioiodide thyroid-imaging techniques and for specific targeting of radioisotopes to the thyroid

20 gland (Levy, O. et al. (1997) Proc. Natl. Acad. Sci. USA 94:5568-5573). SMVT is expressed in the intestinal mucosa, kidney, and placenta, and is implicated in the transport of the water-soluble vitamins, e.g., biotin and pantothenate (Prasad, P.D. et al. (1998) J. Biol. Chem. 273:7501-7506).

The largest and most diverse family of transport proteins is the ATP-binding cassette (ABC) transporters. As a family, ABC transporters can transport substances that differ markedly in chemical

25 structure and size, ranging from small molecules such as ions, sugars, amino acids, peptides, and phospholipids, to lipopeptides, large proteins, and complex hydrophobic drugs. Each ABC transporter consists of four modules: two nucleotide-binding domains (NBDs), which hydrolyze ATP to supply the energy required for transport; and two membrane-spanning domains (MSDs), which may form membrane channels. The NBDs consist of approximately two hundred conserved amino

30 acid residues while the MSDs each contain six putative transmembrane segments. (See, e.g., Saurin, W. et al. (1994) Mol. Microbiol. 12:993-1004; Shani, N. et al. (1996) J. Biol. Chem. 271:8725-8730; Koster, W. and B. Bohm (1992) Mol. Gen. Genet. 232:399-407.) The four ABC transporter modules may be encoded by a single gene, as is the case for the cystic fibrosis transmembrane conductance regulator (CFTR), or by separate genes. When encoded by separate genes, each gene product

contains a single NBD and MSD. These "half-molecules" form homo- and heterodimers, such as Tap1 and Tap2, the endoplasmic reticulum-based major histocompatibility (MHC) peptide transport system associated with antigen processing (Androlewicz, M.J. et al. (1994) Proc. Natl. Acad. Sci. USA 91:12716-12720).

- 5 Several genetic diseases are attributed to defects in ABC transporters, including the following diseases and their corresponding proteins: cystic fibrosis (CFTR, an ion channel; Welsh, M.J. and A.E. Smith (1993) Cell 73:1251-1254); X-linked adrenoleukodystrophy, an inborn error of peroxisomal β -oxidation of very long chain fatty acids (adrenoleukodystrophy protein, ALDP); Zellweger syndrome, an inborn error of peroxisome biogenesis (peroxisomal membrane protein-70, PMP70); and hyperinsulinemic hypoglycemia (sulfonyleurea receptor, SUR). The ABC transporters
10 known as P-glycoproteins, or multidrug resistance (MDR) proteins, are associated with resistance to a wide range of hydrophobic drugs (MDR1; Gottesman, M.M. and I. Pastan (1993) Annu. Rev. Biochem. 62:385-427) or with phosphatidylcholine transport (MDR2; Ruetz, S. and P. Gros (1994) Cell 77:1071-1081). MDR is common in cancer cells, and contributes to low efficacy or failure of
15 chemotherapy (Taglicht, D. and S. Michaelis (1998) Methods Enzymol. 292:131-163). MDR is mediated by transporters, e.g., P-glycoproteins or the multidrug resistance-associated protein MRP, that normally function in the liver, intestines, and kidney to move toxic substances from the cytosol into the bile, intestinal lumen, or urine. In cancerous cells, these transporters extrude
20 chemotherapeutic agents into the extracellular space, thereby conferring drug resistance. Recently, an ABC transporter-type protein was isolated from a human leukemia cell line. This transporter, termed the anthracycline resistance associated protein (GI 1279457, SEQ ID NO:42), is overexpressed in a multidrug resistant leukemia cell sub-line, and has sequence homology with other multidrug-resistance associated proteins including MRP (Longhurst, T.J. et al. (1996) Br. J. Cancer 74:1331-1335).
- 25 Transport of fatty acids across the plasma membrane can occur by diffusion, a high capacity, low affinity process. However, under normal physiological conditions a significant fraction of fatty acid transport appears to occur via a high affinity, low capacity protein-mediated transport process. Fatty acid transport protein (FATP), an integral membrane protein with four transmembrane
30 segments, is expressed in tissues exhibiting high levels of plasma membrane fatty acid flux, such as muscle, heart, and adipose. Expression of FATP is upregulated in 3T3-L1 cells during adipose conversion, and expression in COS7 fibroblasts elevates the cells' uptake of long-chain fatty acids. Expression studies suggest a role for FATP in lipid metabolism, obesity, and type II diabetes mellitus (Hui, T.Y. et al. (1998) J. Biol. Chem. 273:27420-27429).

E1-E2 (or P-type) ATPases constitute a superfamily of cation transporters present in both

prokaryotes and eukaryotes that mediate membrane flux of all biologically relevant cations. These ATPases are postulated to exist in two different conformational states, designated E1 and E2, during the course of the ATP hydrolysis reaction, and to conserve the energy from ATP hydrolysis in the form of an acyl phosphate, primarily an aspartyl phosphate. Members of this family are divided into
5 four major groups; the Ca^{+2} -transporting ATPases, $\text{Na}^{+}/\text{K}^{+}$ -and gastric $\text{H}^{+}/\text{K}^{+}$ -transporting ATPases, plasma membrane H^{+} -transporting ATPases (proton pumps), and the bacterial P-type ATPases (BLOCKS: BL00154, P-type cation-transporting ATPase superfamily signature).

The metabolism of amino acids is complex and highly regulated. While cells are capable of creating most amino acids de novo, the import of amino acids into cells via specific amino acid
10 permease proteins is vital for maintaining the appropriate and complete availability of all necessary amino acids. This is particularly important during cell proliferation and differentiation. In addition to their role as protein building blocks, amino acids also serve as precursors for a variety of other important macromolecules. For example, the hormone thyroxine, the pigment melanin, and the neurotransmitters histamine, epinephrine, and serotonin are produced from various amino acid
15 precursors, including histidine, tyrosine, and tryptophan. A component of sphingolipid formation, sphingosine, is derived from serine. Porphyrin rings, which are components of heme molecules, use glycine as a nitrogen donor. Significant portions of the ring structures of purines and pyrimidines, components of nucleic acids, are formed from the breakdown of numerous amino acids. Amino acids are also important in energy metabolism. Unlike fatty acids and glucose, amino acids cannot be
20 stored in the cell, so excess amino acids are fed into the citric acid cycle to produce energy molecules including fatty acids, ketone bodies, and glucose. Thus, precise control of amino acid metabolism is extremely important to both proliferating and non-proliferating cells.

The E16 gene, cloned from human peripheral blood lymphocytes, encodes a 241 amino acid integral membrane protein with multiple predicted transmembrane domains (Gaugitsch, H.W. et al.
25 (1992) J. Biol. Chem. 267:11267-11273). E16 gene expression is closely linked to cellular activation and division. In myeloid and lymphoid cells, E16 transcripts are rapidly induced and rapidly degraded after stimulation. This pattern of expression resembles the kinetics seen for proto-oncogenes and lymphokines in the T cell system. Elevated levels of E16 expression were detected in colonic, gastric, and breast adenocarcinomas, and in lymphoma, while little or no E16 expression was
30 detected in normal (non-cancerous) human tissues such as adult brain, lung, liver, colon, esophagus, stomach, or kidney, nor in four-month fetal brain, lung, liver, or kidney (Wolf, D.A. et al. (1996) Cancer Res. 56:5012-5022; Gaugitsch et al., supra). E16 was detected in every cell line tested. Its presence in rapidly dividing cell lines and its absence in human tissues with low proliferative potential suggest that E16 is directly involved in the cell division process, where it helps provide important

building blocks for energy metabolism, biochemical synthetic pathways, and protein synthesis.

Post-translational modification of polypeptides occurs in the lumen of the Golgi apparatus. Such modifications include, for example, the addition of sugar molecules by enzymes such as N-acetylglucosaminyltransferase, to produce glycoproteins. The sugar-donating molecules in this
5 reaction are typically nucleotide sugars, such as uridine diphosphate-galactose (UDP-Gal). UDP-Gal and other nucleotide sugars are transported from the cytosol into the Golgi apparatus by specific transporter molecules. The availability of these nucleotide sugars can regulate which glycoproteins are synthesized, and therefore has a significant impact on cellular function (Toma, L. et al. (1996) J. Biol. Chem. 271:3897-3901; Guillen, E. et al. (1998) Proc. Natl. Acad. Sci. USA 95:7888-7892).

10 The discovery of new membrane transport proteins and the polynucleotides encoding them satisfies a need in the art by providing new compositions which are useful in the diagnosis, prevention, and treatment of membrane transport disorders; immune/inflammatory disorders; and cell proliferative disorders including cancer.

15 SUMMARY OF THE INVENTION

The invention features substantially purified polypeptides, membrane transport proteins, referred to collectively as "MTRP" and individually as "MTRP-1," "MTRP-2," "MTRP-3," "MTRP-4," "MTRP-5," "MTRP-6," "MTRP-7," "MTRP-8," "MTRP-9," "MTRP-10," "MTRP-11," "MTRP-12," "MTRP-13," "MTRP-14," "MTRP-15," "MTRP-16," and "MTRP-17." In one aspect, the
20 invention provides a substantially purified polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-17 and fragments thereof. The invention also includes a polypeptide comprising an amino acid sequence that differs by one or more conservative amino acid substitutions from an amino acid sequence selected from the group consisting of SEQ ID NO:1-17.

The invention further provides a substantially purified variant having at least 90% amino acid
25 identity to at least one of the amino acid sequences selected from the group consisting of SEQ ID NO:1-17 and fragments thereof. The invention also provides an isolated and purified polynucleotide encoding the polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-17 and fragments thereof. The invention also includes an isolated and purified polynucleotide variant having at least 90% polynucleotide sequence identity to the polynucleotide
30 encoding the polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-17 and fragments thereof.

Additionally, the invention provides an isolated and purified polynucleotide which hybridizes under stringent conditions to the polynucleotide encoding the polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-17 and fragments thereof. The

invention also provides an isolated and purified polynucleotide having a sequence which is complementary to the polynucleotide encoding the polypeptide comprising the amino acid sequence selected from the group consisting of SEQ ID NO:1-17 and fragments thereof.

5 The invention also provides a method for detecting a polynucleotide in a sample containing nucleic acids, the method comprising the steps of: (a) hybridizing the complement of the polynucleotide sequence to at least one of the polynucleotides of the sample, thereby forming a hybridization complex; and (b) detecting the hybridization complex, wherein the presence of the hybridization complex correlates with the presence of a polynucleotide in the sample. In one aspect, the method further comprises amplifying the polynucleotide prior to hybridization.

10 The invention also provides an isolated and purified polynucleotide comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:18-34 and fragments thereof. The invention further provides an isolated and purified polynucleotide variant having at least 90% polynucleotide sequence identity to the polynucleotide sequence selected from the group consisting of SEQ ID NO:18-34 and fragments thereof. The invention also provides an isolated and
15 purified polynucleotide having a sequence which is complementary to the polynucleotide comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:18-34 and fragments thereof.

The invention further provides an expression vector containing at least a fragment of the polynucleotide encoding the polypeptide comprising an amino acid sequence selected from the group
20 consisting of SEQ ID NO:1-17. In another aspect, the expression vector is contained within a host cell.

The invention also provides a method for producing a polypeptide, the method comprising the steps of: (a) culturing the host cell containing an expression vector containing a polynucleotide of the invention under conditions suitable for the expression of the polypeptide; and (b) recovering the
25 polypeptide from the host cell culture.

The invention also provides a pharmaceutical composition comprising a substantially purified polypeptide having the amino acid sequence selected from the group consisting of SEQ ID NO:1-17 and fragments thereof, in conjunction with a suitable pharmaceutical carrier.

The invention further includes a purified antibody which binds to a polypeptide selected from
30 the group consisting of SEQ ID NO:1-17 and fragments thereof. The invention also provides a purified agonist and a purified antagonist to the polypeptide.

The invention also provides a method for treating or preventing a disorder associated with decreased expression or activity of MTRP, the method comprising administering to a subject in need of such treatment an effective amount of a pharmaceutical composition comprising a substantially

purified polypeptide having the amino acid sequence selected from the group consisting of SEQ ID NO:1-17 and fragments thereof, in conjunction with a suitable pharmaceutical carrier.

The invention also provides a method for treating or preventing a disorder associated with increased expression or activity of MTRP, the method comprising administering to a subject in need of such treatment an effective amount of an antagonist of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-17 and fragments thereof.

BRIEF DESCRIPTION OF THE FIGURES AND TABLES

Figures 1A, 1B, 1C, and 1D show the amino acid sequence alignment between MTRP-3 (Incyte Clone ID 1720440; SEQ ID NO:3) and mouse fatty acid transport protein (GI 2612939; SEQ ID NO:35), produced using the multisequence alignment program of LASERGENE software (DNASTAR, Madison WI).

Figures 2A, 2B, 2C, and 2D show the amino acid sequence alignment between MTRP-4 (Incyte Clone ID 2274290; SEQ ID NO:4) and Schistosoma mansoni SMDR1 (GI 425474; SEQ ID NO:36), produced using the multisequence alignment program of LASERGENE software (DNASTAR).

Figures 3A, 3B, 3C, and 3D show the amino acid sequence alignment between MTRP-5 (Incyte Clone ID 2740029; SEQ ID NO:5) and rat sodium-dependent multivitamin transporter (GI 3015617; SEQ ID NO:37), produced using the multisequence alignment program of LASERGENE software (DNASTAR).

Table 1 shows polypeptide and nucleotide sequence identification numbers (SEQ ID NOs), clone identification numbers (clone IDs), cDNA libraries, and cDNA fragments used to assemble full-length sequences encoding MTRP.

Table 2 shows features of each polypeptide sequence, including potential motifs, homologous sequences, and methods, algorithms, and searchable databases used for analysis of MTRP.

Table 3 shows the tissue-specific expression patterns of each nucleic acid sequence as determined by northern analysis; diseases, disorders, or conditions associated with these tissues; and the vector into which each cDNA was cloned.

Table 4 describes the tissues used to construct the cDNA libraries from which cDNA clones encoding MTRP were isolated.

Table 5 shows the tools, programs, and algorithms used to analyze MTRP, along with applicable descriptions, references, and threshold parameters.

DESCRIPTION OF THE INVENTION

Before the present proteins, nucleotide sequences, and methods are described, it is understood that this invention is not limited to the particular machines, materials and methods described, as these may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims.

It must be noted that as used herein and in the appended claims, the singular forms "a," "an," and "the" include plural reference unless the context clearly dictates otherwise. Thus, for example, a reference to "a host cell" includes a plurality of such host cells, and a reference to "an antibody" is a reference to one or more antibodies and equivalents thereof known to those skilled in the art, and so forth.

Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any machines, materials, and methods similar or equivalent to those described herein can be used to practice or test the present invention, the preferred machines, materials and methods are now described. All publications mentioned herein are cited for the purpose of describing and disclosing the cell lines, protocols, reagents and vectors which are reported in the publications and which might be used in connection with the invention. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

DEFINITIONS

"MTRP" refers to the amino acid sequences of substantially purified MTRP obtained from any species, particularly a mammalian species, including bovine, ovine, porcine, murine, equine, and human, and from any source, whether natural, synthetic, semi-synthetic, or recombinant.

The term "agonist" refers to a molecule which intensifies or mimics the biological activity of MTRP. Agonists may include proteins, nucleic acids, carbohydrates, small molecules, or any other compound or composition which modulates the activity of MTRP either by directly interacting with MTRP or by acting on components of the biological pathway in which MTRP participates.

An "allelic variant" is an alternative form of the gene encoding MTRP. Allelic variants may result from at least one mutation in the nucleic acid sequence and may result in altered mRNAs or in polypeptides whose structure or function may or may not be altered. A gene may have none, one, or many allelic variants of its naturally occurring form. Common mutational changes which give rise to allelic variants are generally ascribed to natural deletions, additions, or substitutions of nucleotides. Each of these types of changes may occur alone, or in combination with the others, one or more times in a given sequence.

"Altered" nucleic acid sequences encoding MTRP include those sequences with deletions,

insertions, or substitutions of different nucleotides, resulting in a polypeptide the same as MTRP or a polypeptide with at least one functional characteristic of MTRP. Included within this definition are polymorphisms which may or may not be readily detectable using a particular oligonucleotide probe of the polynucleotide encoding MTRP, and improper or unexpected hybridization to allelic variants, with a locus other than the normal chromosomal locus for the polynucleotide sequence encoding MTRP. The encoded protein may also be "altered," and may contain deletions, insertions, or substitutions of amino acid residues which produce a silent change and result in a functionally equivalent MTRP. Deliberate amino acid substitutions may be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity, and/or the amphipathic nature of the residues, as long as the biological or immunological activity of MTRP is retained. For example, negatively charged amino acids may include aspartic acid and glutamic acid, and positively charged amino acids may include lysine and arginine. Amino acids with uncharged polar side chains having similar hydrophilicity values may include: asparagine and glutamine; and serine and threonine. Amino acids with uncharged side chains having similar hydrophilicity values may include: leucine, isoleucine, and valine; glycine and alanine; and phenylalanine and tyrosine.

The terms "amino acid" and "amino acid sequence" refer to an oligopeptide, peptide, polypeptide, or protein sequence, or a fragment of any of these, and to naturally occurring or synthetic molecules. Where "amino acid sequence" is recited to refer to an amino acid sequence of a naturally occurring protein molecule, "amino acid sequence" and like terms are not meant to limit the amino acid sequence to the complete native amino acid sequence associated with the recited protein molecule.

"Amplification" relates to the production of additional copies of a nucleic acid sequence. Amplification is generally carried out using polymerase chain reaction (PCR) technologies well known in the art.

The term "antagonist" refers to a molecule which inhibits or attenuates the biological activity of MTRP. Antagonists may include proteins such as antibodies, nucleic acids, carbohydrates, small molecules, or any other compound or composition which modulates the activity of MTRP either by directly interacting with MTRP or by acting on components of the biological pathway in which MTRP participates.

The term "antibody" refers to intact immunoglobulin molecules as well as to fragments thereof, such as Fab, F(ab')₂, and Fv fragments, which are capable of binding an epitopic determinant. Antibodies that bind MTRP polypeptides can be prepared using intact polypeptides or using fragments containing small peptides of interest as the immunizing antigen. The polypeptide or oligopeptide used to immunize an animal (e.g., a mouse, a rat, or a rabbit) can be derived from the

translation of RNA, or synthesized chemically, and can be conjugated to a carrier protein if desired. Commonly used carriers that are chemically coupled to peptides include bovine serum albumin, thyroglobulin, and keyhole limpet hemocyanin (KLH). The coupled peptide is then used to immunize the animal.

5 The term "antigenic determinant" refers to that region of a molecule (i.e., an epitope) that makes contact with a particular antibody. When a protein or a fragment of a protein is used to immunize a host animal, numerous regions of the protein may induce the production of antibodies which bind specifically to antigenic determinants (particular regions or three-dimensional structures on the protein). An antigenic determinant may compete with the intact antigen (i.e., the immunogen
10 used to elicit the immune response) for binding to an antibody.

 The term "antisense" refers to any composition containing a nucleic acid sequence which is complementary to the "sense" strand of a specific nucleic acid sequence. Antisense molecules may be produced by any method including synthesis or transcription. Once introduced into a cell, the complementary nucleotides combine with natural sequences produced by the cell to form duplexes
15 and to block either transcription or translation. The designation "negative" or "minus" can refer to the antisense strand, and the designation "positive" or "plus" can refer to the sense strand.

 The term "biologically active" refers to a protein having structural, regulatory, or biochemical functions of a naturally occurring molecule. Likewise, "immunologically active" refers to the capability of the natural, recombinant, or synthetic MTRP, or of any oligopeptide thereof, to induce a
20 specific immune response in appropriate animals or cells and to bind with specific antibodies.

 The terms "complementary" and "complementarity" refer to the natural binding of polynucleotides by base pairing. For example, the sequence "5' A-G-T 3'" bonds to the complementary sequence "3' T-C-A 5'." Complementarity between two single-stranded molecules may be "partial," such that only some of the nucleic acids bind, or it may be "complete," such that
25 total complementarity exists between the single stranded molecules. The degree of complementarity between nucleic acid strands has significant effects on the efficiency and strength of the hybridization between the nucleic acid strands. This is of particular importance in amplification reactions, which depend upon binding between nucleic acid strands, and in the design and use of peptide nucleic acid (PNA) molecules.

30 A "composition comprising a given polynucleotide sequence" and a "composition comprising a given amino acid sequence" refer broadly to any composition containing the given polynucleotide or amino acid sequence. The composition may comprise a dry formulation or an aqueous solution. Compositions comprising polynucleotide sequences encoding MTRP or fragments of MTRP may be employed as hybridization probes. The probes may be stored in freeze-dried form and may be

associated with a stabilizing agent such as a carbohydrate. In hybridizations, the probe may be deployed in an aqueous solution containing salts (e.g., NaCl), detergents (e.g., sodium dodecyl sulfate; SDS), and other components (e.g., Denhardt's solution, dry milk, salmon sperm DNA, etc.).

"Consensus sequence" refers to a nucleic acid sequence which has been resequenced to resolve uncalled bases, extended using the XL-PCR kit (Perkin-Elmer, Norwalk CT) in the 5' and/or the 3' direction, and resequenced, or which has been assembled from the overlapping sequences of one or more Incyte Clones and, in some cases, one or more public domain ESTs, using a computer program for fragment assembly, such as the GELVIEW fragment assembly system (GCG, Madison WI). Some sequences have been both extended and assembled to produce the consensus sequence.

"Conservative amino acid substitutions" are those substitutions that, when made, least interfere with the properties of the original protein, i.e., the structure and especially the function of the protein is conserved and not significantly changed by such substitutions. The table below shows amino acids which may be substituted for an original amino acid in a protein and which are regarded as conservative amino acid substitutions.

| | Original Residue | Conservative Substitution |
|----|------------------|---------------------------|
| 15 | Ala | Gly, Ser |
| | Arg | His, Lys |
| | Asn | Asp, Gln, His |
| | Asp | Asn, Glu |
| 20 | Cys | Ala, Ser |
| | Gln | Asn, Glu, His |
| | Glu | Asp, Gln, His |
| | Gly | Ala |
| | His | Asn, Arg, Gln, Glu |
| 25 | Ile | Leu, Val |
| | Leu | Ile, Val |
| | Lys | Arg, Gln, Glu |
| | Met | Leu, Ile |
| | Phe | His, Met, Leu, Trp, Tyr |
| 30 | Ser | Cys, Thr |
| | Thr | Ser, Val |
| | Trp | Phe, Tyr |
| | Tyr | His, Phe, Trp |
| | Val | Ile, Leu, Thr |

35

Conservative amino acid substitutions generally maintain (a) the structure of the polypeptide backbone in the area of the substitution, for example, as a beta sheet or alpha helical conformation, (b) the charge or hydrophobicity of the molecule at the site of the substitution, and/or (c) the bulk of the side chain.

40 A "deletion" refers to a change in the amino acid or nucleotide sequence that results in the absence of one or more amino acid residues or nucleotides.

The term "derivative" refers to the chemical modification of a polypeptide sequence, or a polynucleotide sequence. Chemical modifications of a polynucleotide sequence can include, for example, replacement of hydrogen by an alkyl, acyl, hydroxyl, or amino group. A derivative polynucleotide encodes a polypeptide which retains at least one biological or immunological function of the natural molecule. A derivative polypeptide is one modified by glycosylation, pegylation, or any similar process that retains at least one biological or immunological function of the polypeptide from which it was derived.

A "fragment" is a unique portion of MTRP or the polynucleotide encoding MTRP which is identical in sequence to but shorter in length than the parent sequence. A fragment may comprise up to the entire length of the defined sequence, minus one nucleotide/amino acid residue. For example, a fragment may comprise from 5 to 1000 contiguous nucleotides or amino acid residues. A fragment used as a probe, primer, antigen, therapeutic molecule, or for other purposes, may be at least 5, 10, 15, 20, 25, 30, 40, 50, 60, 75, 100, 150, 250 or at least 500 contiguous nucleotides or amino acid residues in length. Fragments may be preferentially selected from certain regions of a molecule. For example, a polypeptide fragment may comprise a certain length of contiguous amino acids selected from the first 250 or 500 amino acids (or first 25% or 50% of a polypeptide) as shown in a certain defined sequence. Clearly these lengths are exemplary, and any length that is supported by the specification, including the Sequence Listing, tables, and figures, may be encompassed by the present embodiments.

A fragment of SEQ ID NO:18-34 comprises a region of unique polynucleotide sequence that specifically identifies SEQ ID NO:18-34, for example, as distinct from any other sequence in the same genome. A fragment of SEQ ID NO:18-34 is useful, for example, in hybridization and amplification technologies and in analogous methods that distinguish SEQ ID NO:18-34 from related polynucleotide sequences. The precise length of a fragment of SEQ ID NO:18-34 and the region of SEQ ID NO:18-34 to which the fragment corresponds are routinely determinable by one of ordinary skill in the art based on the intended purpose for the fragment.

A fragment of SEQ ID NO:1-17 is encoded by a fragment of SEQ ID NO:18-34. A fragment of SEQ ID NO:1-17 comprises a region of unique amino acid sequence that specifically identifies SEQ ID NO:1-17. For example, a fragment of SEQ ID NO:1-17 is useful as an immunogenic peptide for the development of antibodies that specifically recognize SEQ ID NO:1-17. The precise length of a fragment of SEQ ID NO:1-17 and the region of SEQ ID NO:1-17 to which the fragment corresponds are routinely determinable by one of ordinary skill in the art based on the intended purpose for the fragment.

The term "similarity" refers to a degree of complementarity. There may be partial similarity or complete similarity. The word "identity" may substitute for the word "similarity." A partially

complementary sequence that at least partially inhibits an identical sequence from hybridizing to a target nucleic acid is referred to as "substantially similar." The inhibition of hybridization of the completely complementary sequence to the target sequence may be examined using a hybridization assay (Southern or northern blot, solution hybridization, and the like) under conditions of reduced stringency. A substantially similar sequence or hybridization probe will compete for and inhibit the binding of a completely similar (identical) sequence to the target sequence under conditions of reduced stringency. This is not to say that conditions of reduced stringency are such that non-specific binding is permitted, as reduced stringency conditions require that the binding of two sequences to one another be a specific (i.e., a selective) interaction. The absence of non-specific binding may be tested by the use of a second target sequence which lacks even a partial degree of complementarity (e.g., less than about 30% similarity or identity). In the absence of non-specific binding, the substantially similar sequence or probe will not hybridize to the second non-complementary target sequence.

The phrases "percent identity" and "% identity," as applied to polynucleotide sequences, refer to the percentage of residue matches between at least two polynucleotide sequences aligned using a standardized algorithm. Such an algorithm may insert, in a standardized and reproducible way, gaps in the sequences being compared in order to optimize alignment between two sequences, and therefore achieve a more meaningful comparison of the two sequences.

Percent identity between polynucleotide sequences may be determined using the default parameters of the CLUSTAL V algorithm as incorporated into the MEGALIGN version 3.12e sequence alignment program. This program is part of the LASERGENE software package, a suite of molecular biological analysis programs (DNASTAR, Madison WI). CLUSTAL V is described in Higgins, D.G. and P.M. Sharp (1989) CABIOS 5:151-153 and in Higgins, D.G. et al. (1992) CABIOS 8:189-191. For pairwise alignments of polynucleotide sequences, the default parameters are set as follows: Ktuple=2, gap penalty=5, window=4, and "diagonals saved"=4. The "weighted" residue weight table is selected as the default. Percent identity is reported by CLUSTAL V as the "percent similarity" between aligned polynucleotide sequence pairs.

Alternatively, a suite of commonly used and freely available sequence comparison algorithms is provided by the National Center for Biotechnology Information (NCBI) Basic Local Alignment Search Tool (BLAST) (Altschul, S.F. et al. (1990) J. Mol. Biol. 215:403-410), which is available from several sources, including the NCBI, Bethesda, MD, and on the Internet at <http://www.ncbi.nlm.nih.gov/BLAST/>. The BLAST software suite includes various sequence analysis programs including "blastn," that is used to align a known polynucleotide sequence with other polynucleotide sequences from a variety of databases. Also available is a tool called "BLAST 2

Sequences" that is used for direct pairwise comparison of two nucleotide sequences. "BLAST 2 Sequences" can be accessed and used interactively at <http://www.ncbi.nlm.nih.gov/gorf/bl2.html>. The "BLAST 2 Sequences" tool can be used for both blastn and blastp (discussed below). BLAST programs are commonly used with gap and other parameters set to default settings. For example, to

5 compare two nucleotide sequences, one may use blastn with the "BLAST 2 Sequences" tool Version 2.0.9 (May-07-1999) set at default parameters. Such default parameters may be, for example:

Matrix: BLOSUM62

Reward for match: 1

Penalty for mismatch: -2

10 *Open Gap: 5 and Extension Gap: 2 penalties*

Gap x drop-off: 50

Expect: 10

Word Size: 11

Filter: on

15 Percent identity may be measured over the length of an entire defined sequence, for example, as defined by a particular SEQ ID number, or may be measured over a shorter length, for example, over the length of a fragment taken from a larger, defined sequence, for instance, a fragment of at least 20, at least 30, at least 40, at least 50, at least 70, at least 100, or at least 200 contiguous nucleotides. Such lengths are exemplary only, and it is understood that any fragment length supported

20 by the sequences shown herein, in the tables, figures, or Sequence Listing, may be used to describe a length over which percentage identity may be measured.

Nucleic acid sequences that do not show a high degree of identity may nevertheless encode similar amino acid sequences due to the degeneracy of the genetic code. It is understood that changes in a nucleic acid sequence can be made using this degeneracy to produce multiple nucleic acid

25 sequences that all encode substantially the same protein.

The phrases "percent identity" and "% identity," as applied to polypeptide sequences, refer to the percentage of residue matches between at least two polypeptide sequences aligned using a standardized algorithm. Methods of polypeptide sequence alignment are well-known. Some alignment methods take into account conservative amino acid substitutions. Such conservative

30 substitutions, explained in more detail above, generally preserve the hydrophobicity and acidity at the site of substitution, thus preserving the structure (and therefore function) of the polypeptide.

Percent identity between polypeptide sequences may be determined using the default parameters of the CLUSTAL V algorithm as incorporated into the MEGALIGN version 3.12e sequence alignment program (described and referenced above). For pairwise alignments of

polypeptide sequences using CLUSTAL V, the default parameters are set as follows: Ktuple=1, gap penalty=3, window=5, and "diagonals saved"=5. The PAM250 matrix is selected as the default residue weight table. As with polynucleotide alignments, the percent identity is reported by CLUSTAL V as the "percent similarity" between aligned polypeptide sequence pairs.

- 5 Alternatively the NCBI BLAST software suite may be used. For example, for a pairwise comparison of two polypeptide sequences, one may use the "BLAST 2 Sequences" tool Version 2.0.9 (May-07-1999) with blastp set at default parameters. Such default parameters may be, for example:

Matrix: BLOSUM62

Open Gap: 11 and Extension Gap: 1 penalties

- 10 *Gap x drop-off: 50*

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- Percent identity may be measured over the length of an entire defined polypeptide sequence, for example, as defined by a particular SEQ ID number, or may be measured over a shorter length, for example, over the length of a fragment taken from a larger, defined polypeptide sequence, for instance, a fragment of at least 15, at least 20, at least 30, at least 40, at least 50, at least 70 or at least 150 contiguous residues. Such lengths are exemplary only, and it is understood that any fragment length supported by the sequences shown herein, in the tables, figures or Sequence Listing, may be used to describe a length over which percentage identity may be measured.
- 15
20

"Human artificial chromosomes" (HACs) are linear microchromosomes which may contain DNA sequences of about 6 kb to 10 Mb in size, and which contain all of the elements required for stable mitotic chromosome segregation and maintenance.

- The term "humanized antibody" refers to antibody molecules in which the amino acid sequence in the non-antigen binding regions has been altered so that the antibody more closely resembles a human antibody, and still retains its original binding ability.
- 25

- "Hybridization" refers to the process by which a polynucleotide strand anneals with a complementary strand through base pairing under defined hybridization conditions. Specific hybridization is an indication that two nucleic acid sequences share a high degree of identity. Specific hybridization complexes form under permissive annealing conditions and remain hybridized after the "washing" step(s). The washing step(s) is particularly important in determining the stringency of the hybridization process, with more stringent conditions allowing less non-specific binding, i.e., binding between pairs of nucleic acid strands that are not perfectly matched. Permissive conditions for annealing of nucleic acid sequences are routinely determinable by one of ordinary skill in the art and
- 30

may be consistent among hybridization experiments, whereas wash conditions may be varied among experiments to achieve the desired stringency, and therefore hybridization specificity. Permissive annealing conditions occur, for example, at 68°C in the presence of about 6 x SSC, about 1% (w/v) SDS, and about 100 µg/ml denatured salmon sperm DNA.

5 Generally, stringency of hybridization is expressed, in part, with reference to the temperature under which the wash step is carried out. Generally, such wash temperatures are selected to be about 5°C to 20°C lower than the thermal melting point (T_m) for the specific sequence at a defined ionic strength and pH. The T_m is the temperature (under defined ionic strength and pH) at which 50% of the target sequence hybridizes to a perfectly matched probe. An equation for calculating T_m and
10 conditions for nucleic acid hybridization are well known and can be found in Sambrook et al., 1989, Molecular Cloning: A Laboratory Manual, 2nd ed., vol. 1-3, Cold Spring Harbor Press, Plainview NY; specifically see volume 2, chapter 9.

High stringency conditions for hybridization between polynucleotides of the present invention include wash conditions of 68°C in the presence of about 0.2 x SSC and about 0.1% SDS, for 1 hour.
15 Alternatively, temperatures of about 65°C, 60°C, 55°C, or 42°C may be used. SSC concentration may be varied from about 0.1 to 2 x SSC, with SDS being present at about 0.1%. Typically, blocking reagents are used to block non-specific hybridization. Such blocking reagents include, for instance, denatured salmon sperm DNA at about 100-200 µg/ml. Organic solvent, such as formamide at a concentration of about 35-50% v/v, may also be used under particular circumstances, such as for
20 RNA:DNA hybridizations. Useful variations on these wash conditions will be readily apparent to those of ordinary skill in the art. Hybridization, particularly under high stringency conditions, may be suggestive of evolutionary similarity between the nucleotides. Such similarity is strongly indicative of a similar role for the nucleotides and their encoded polypeptides.

The term "hybridization complex" refers to a complex formed between two nucleic acid
25 sequences by virtue of the formation of hydrogen bonds between complementary bases. A hybridization complex may be formed in solution (e.g., C_0t or R_0t analysis) or formed between one nucleic acid sequence present in solution and another nucleic acid sequence immobilized on a solid support (e.g., paper, membranes, filters, chips, pins or glass slides, or any other appropriate substrate to which cells or their nucleic acids have been fixed).

30 The words "insertion" and "addition" refer to changes in an amino acid or nucleotide sequence resulting in the addition of one or more amino acid residues or nucleotides, respectively.

"Immune response" can refer to conditions associated with inflammation, trauma, immune disorders, or infectious or genetic disease, etc. These conditions can be characterized by expression of various factors, e.g., cytokines, chemokines, and other signaling molecules, which may affect

cellular and systemic defense systems.

The term "microarray" refers to an arrangement of distinct polynucleotides on a substrate.

The terms "element" and "array element" in a microarray context, refer to hybridizable polynucleotides arranged on the surface of a substrate.

5 The term "modulate" refers to a change in the activity of MTRP. For example, modulation may cause an increase or a decrease in protein activity, binding characteristics, or any other biological, functional, or immunological properties of MTRP.

The phrases "nucleic acid" and "nucleic acid sequence" refer to a nucleotide, oligonucleotide, polynucleotide, or any fragment thereof. These phrases also refer to DNA or RNA of genomic or
10 synthetic origin which may be single-stranded or double-stranded and may represent the sense or the antisense strand, to peptide nucleic acid (PNA), or to any DNA-like or RNA-like material.

"Operably linked" refers to the situation in which a first nucleic acid sequence is placed in a functional relationship with the second nucleic acid sequence. For instance, a promoter is operably linked to a coding sequence if the promoter affects the transcription or expression of the coding
15 sequence. Generally, operably linked DNA sequences may be in close proximity or contiguous and, where necessary to join two protein coding regions, in the same reading frame.

"Peptide nucleic acid" (PNA) refers to an antisense molecule or anti-gene agent which comprises an oligonucleotide of at least about 5 nucleotides in length linked to a peptide backbone of amino acid residues ending in lysine. The terminal lysine confers solubility to the composition.
20 PNAs preferentially bind complementary single stranded DNA or RNA and stop transcript elongation, and may be pegylated to extend their lifespan in the cell.

"Probe" refers to nucleic acid sequences encoding MTRP, their complements, or fragments thereof, which are used to detect identical, allelic or related nucleic acid sequences. Probes are isolated oligonucleotides or polynucleotides attached to a detectable label or reporter molecule.
25 Typical labels include radioactive isotopes, ligands, chemiluminescent agents, and enzymes.

"Primers" are short nucleic acids, usually DNA oligonucleotides, which may be annealed to a target polynucleotide by complementary base-pairing. The primer may then be extended along the target DNA strand by a DNA polymerase enzyme. Primer pairs can be used for amplification (and identification) of a nucleic acid sequence, e.g., by the polymerase chain reaction (PCR).

30 Probes and primers as used in the present invention typically comprise at least 15 contiguous nucleotides of a known sequence. In order to enhance specificity, longer probes and primers may also be employed, such as probes and primers that comprise at least 20, 25, 30, 40, 50, 60, 70, 80, 90, 100, or at least 150 consecutive nucleotides of the disclosed nucleic acid sequences. Probes and primers may be considerably longer than these examples, and it is understood that any length supported by the

specification, including the tables, figures, and Sequence Listing, may be used.

Methods for preparing and using probes and primers are described in the references, for example Sambrook et al., 1989, Molecular Cloning: A Laboratory Manual, 2nd ed., vol. 1-3, Cold Spring Harbor Press, Plainview NY; Ausubel et al., 1987, Current Protocols in Molecular Biology,
5 Greene Publ. Assoc. & Wiley-Intersciences, New York NY; Innis et al., 1990, PCR Protocols, A Guide to Methods and Applications, Academic Press, San Diego CA. PCR primer pairs can be derived from a known sequence, for example, by using computer programs intended for that purpose such as Primer (Version 0.5, 1991, Whitehead Institute for Biomedical Research, Cambridge MA).

Oligonucleotides for use as primers are selected using software known in the art for such
10 purpose. For example, OLIGO 4.06 software is useful for the selection of PCR primer pairs of up to 100 nucleotides each, and for the analysis of oligonucleotides and larger polynucleotides of up to 5,000 nucleotides from an input polynucleotide sequence of up to 32 kilobases. Similar primer selection programs have incorporated additional features for expanded capabilities. For example, the PrimOU primer selection program (available to the public from the Genome Center at University of
15 Texas South West Medical Center, Dallas TX) is capable of choosing specific primers from megabase sequences and is thus useful for designing primers on a genome-wide scope. The Primer3 primer selection program (available to the public from the Whitehead Institute/MIT Center for Genome Research, Cambridge MA) allows the user to input a "mispriming library," in which sequences to avoid as primer binding sites are user-specified. Primer3 is useful, in particular, for the selection of
20 oligonucleotides for microarrays. (The source code for the latter two primer selection programs may also be obtained from their respective sources and modified to meet the user's specific needs.) The PrimeGen program (available to the public from the UK Human Genome Mapping Project Resource Centre, Cambridge UK) designs primers based on multiple sequence alignments, thereby allowing selection of primers that hybridize to either the most conserved or least conserved regions of aligned
25 nucleic acid sequences. Hence, this program is useful for identification of both unique and conserved oligonucleotides and polynucleotide fragments. The oligonucleotides and polynucleotide fragments identified by any of the above selection methods are useful in hybridization technologies, for example, as PCR or sequencing primers, microarray elements, or specific probes to identify fully or partially complementary polynucleotides in a sample of nucleic acids. Methods of oligonucleotide
30 selection are not limited to those described above.

A "recombinant nucleic acid" is a sequence that is not naturally occurring or has a sequence that is made by an artificial combination of two or more otherwise separated segments of sequence. This artificial combination is often accomplished by chemical synthesis or, more commonly, by the artificial manipulation of isolated segments of nucleic acids, e.g., by genetic engineering techniques

such as those described in Sambrook, supra. The term recombinant includes nucleic acids that have been altered solely by addition, substitution, or deletion of a portion of the nucleic acid. Frequently, a recombinant nucleic acid may include a nucleic acid sequence operably linked to a promoter sequence. Such a recombinant nucleic acid may be part of a vector that is used, for example, to
5 transform a cell.

Alternatively, such recombinant nucleic acids may be part of a viral vector, e.g., based on a vaccinia virus, that could be used to vaccinate a mammal wherein the recombinant nucleic acid is expressed, inducing a protective immunological response in the mammal.

The term "sample" is used in its broadest sense. A sample suspected of containing nucleic
10 acids encoding MTRP, or fragments thereof, or MTRP itself, may comprise a bodily fluid; an extract from a cell, chromosome, organelle, or membrane isolated from a cell; a cell; genomic DNA, RNA, or cDNA, in solution or bound to a substrate; a tissue; a tissue print; etc.

The terms "specific binding" and "specifically binding" refer to that interaction between a protein or peptide and an agonist, an antibody, an antagonist, a small molecule, or any natural or
15 synthetic binding composition. The interaction is dependent upon the presence of a particular structure of the protein, e.g., the antigenic determinant or epitope, recognized by the binding molecule. For example, if an antibody is specific for epitope "A," the presence of a polypeptide containing the epitope A, or the presence of free unlabeled A, in a reaction containing free labeled A and the antibody will reduce the amount of labeled A that binds to the antibody.

20 The term "substantially purified" refers to nucleic acid or amino acid sequences that are removed from their natural environment and are isolated or separated, and are at least about 60% free, preferably about 75% free, and most preferably about 90% free from other components with which they are naturally associated.

A "substitution" refers to the replacement of one or more amino acids or nucleotides by
25 different amino acids or nucleotides, respectively.

"Substrate" refers to any suitable rigid or semi-rigid support including membranes, filters, chips, slides, wafers, fibers, magnetic or nonmagnetic beads, gels, tubing, plates, polymers, microparticles and capillaries. The substrate can have a variety of surface forms, such as wells, trenches, pins, channels and pores, to which polynucleotides or polypeptides are bound.

30 "Transformation" describes a process by which exogenous DNA enters and changes a recipient cell. Transformation may occur under natural or artificial conditions according to various methods well known in the art, and may rely on any known method for the insertion of foreign nucleic acid sequences into a prokaryotic or eukaryotic host cell. The method for transformation is selected based on the type of host cell being transformed and may include, but is not limited to, viral infection,

electroporation, heat shock, lipofection, and particle bombardment. The term "transformed" cells includes stably transformed cells in which the inserted DNA is capable of replication either as an autonomously replicating plasmid or as part of the host chromosome, as well as transiently transformed cells which express the inserted DNA or RNA for limited periods of time.

5 A "variant" of a particular nucleic acid sequence is defined as a nucleic acid sequence having at least 40% sequence identity to the particular nucleic acid sequence over a certain length of one of the nucleic acid sequences using blastn with the "BLAST 2 Sequences" tool Version 2.0.9 (May-07-1999) set at default parameters. Such a pair of nucleic acids may show, for example, at least 50%, at least 60%, at least 70%, at least 80%, at least 85%, at least 90%, at least 95% or at least 98% or
10 greater sequence identity over a certain defined length. A variant may be described as, for example, an "allelic" (as defined above), "splice," "species," or "polymorphic" variant. A splice variant may have significant identity to a reference molecule, but will generally have a greater or lesser number of polynucleotides due to alternate splicing of exons during mRNA processing. The corresponding polypeptide may possess additional functional domains or lack domains that are present in the
15 reference molecule. Species variants are polynucleotide sequences that vary from one species to another. The resulting polypeptides generally will have significant amino acid identity relative to each other. A polymorphic variant is a variation in the polynucleotide sequence of a particular gene between individuals of a given species. Polymorphic variants also may encompass "single nucleotide polymorphisms" (SNPs) in which the polynucleotide sequence varies by one nucleotide base. The
20 presence of SNPs may be indicative of, for example, a certain population, a disease state, or a propensity for a disease state.

A "variant" of a particular polypeptide sequence is defined as a polypeptide sequence having at least 40% sequence identity to the particular polypeptide sequence over a certain length of one of the polypeptide sequences using blastp with the "BLAST 2 Sequences" tool Version 2.0.9 (May-07-
25 1999) set at default parameters. Such a pair of polypeptides may show, for example, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, or at least 98% or greater sequence identity over a certain defined length of one of the polypeptides.

THE INVENTION

The invention is based on the discovery of new human membrane transport proteins (MTRP),
30 the polynucleotides encoding MTRP, and the use of these compositions for the diagnosis, treatment, or prevention of membrane transport disorders; immune/inflammatory disorders; and cell proliferative disorders including cancer.

Table 1 lists the Incyte clones used to assemble full length nucleotide sequences encoding MTRP. Columns 1 and 2 show the sequence identification numbers (SEQ ID NOs) of the polypeptide

and nucleotide sequences, respectively. Column 3 shows the clone IDs of the Incyte clones in which nucleic acids encoding each MTRP were identified, and column 4 shows the cDNA libraries from which these clones were isolated. Column 5 shows Incyte clones and their corresponding cDNA libraries. Clones for which cDNA libraries are not indicated were derived from pooled cDNA libraries. The Incyte clones in column 5 were used to assemble the consensus nucleotide sequence of each MTRP and are useful as fragments in hybridization technologies.

The columns of Table 2 show various properties of each of the polypeptides of the invention: column 1 references the SEQ ID NO; column 2 shows the number of amino acid residues in each polypeptide; column 3 shows potential phosphorylation sites; column 4 shows potential glycosylation sites; column 5 shows the amino acid residues comprising signature sequences and motifs; column 6 shows homologous sequences as identified by BLAST analysis; and column 7 shows analytical methods and in some cases, searchable databases to which the analytical methods were applied. The methods of column 7 were used to characterize each polypeptide through sequence homology and protein motifs.

As shown in Figures 1A, 1B, 1C, and 1D, MTRP-3 has chemical and structural similarity with mouse fatty acid transport protein (FATP; GI 2612939; SEQ ID NO:35). In particular, MTRP-3 and FATP share 65% identity. As shown in Figures 2A, 2B, 2C, and 2D, MTRP-4 has chemical and structural similarity with Schistosoma mansoni ATP-binding cassette family protein, SMDR-1 (GI 425474; SEQ ID NO:36). In particular, MTRP-4 and SMDR-1 share 38% identity. As shown in Figures 3A, 3B, 3C, and 3D, MTRP-5 has chemical and structural similarity with rat sodium-dependent multivitamin transporter (SMVT; GI 3015617; SEQ ID NO:37). In particular, MTRP-5 and SMVT share 82% identity.

The columns of Table 3 show the tissue-specificity and diseases, disorders, or conditions associated with nucleotide sequences encoding MTRP. The first column of Table 3 lists the nucleotide SEQ ID NOs. Column 2 lists tissue categories which express MTRP as a fraction of total tissues expressing MTRP. Column 3 lists diseases, disorders, or conditions associated with those tissues expressing MTRP as a fraction of total tissues expressing MTRP. Column 4 lists the vectors used to subclone each cDNA library.

Of particular note are the expression patterns of SEQ ID NO:30 and SEQ ID NO:31. SEQ ID NO:30 is expressed in only five libraries, of which at least four (80%) are associated with cell proliferation and at least one (20%) with inflammation. Two (40%) of the five libraries are associated with cardiovascular tissue, and one each (20%) with gastrointestinal, nervous, and reproductive tissues. SEQ ID NO:31 is expressed in only four libraries, of which at least three (75%) are associated with cell proliferation and at least two (50%) with inflammation or the immune response.

Two (50%) of the four libraries are associated with hematopoietic/immune tissue, and one each (25%) with cardiovascular and reproductive tissues.

The following fragments of the nucleotide sequences encoding MTRP are useful, for example, in hybridization or amplification technologies to identify SEQ ID NO:18-34 and to distinguish between SEQ ID NO:18-34 and related polynucleotide sequences. The useful fragments include the fragment of SEQ ID NO:18 from about nucleotide 110 to about nucleotide 154; the fragment of SEQ ID NO:19 from about nucleotide 759 to about nucleotide 839; the fragment of SEQ ID NO:20 from about nucleotide 1531 to about nucleotide 1578; the fragment of SEQ ID NO:21 from about nucleotide 538 to about nucleotide 597; the fragment of SEQ ID NO:22 from about nucleotide 2241 to about nucleotide 2294; the fragment of SEQ ID NO:23 from about nucleotide 116 to about nucleotide 145; the fragment of SEQ ID NO:24 from about nucleotide 60 to about nucleotide 89; the fragment of SEQ ID NO:25 from about nucleotide 160 to about nucleotide 189; the fragment of SEQ ID NO:26 from about nucleotide 763 to about nucleotide 792; the fragment of SEQ ID NO:27 from about nucleotide 43 to about nucleotide 72; the fragment of SEQ ID NO:28 from about nucleotide 361 to about nucleotide 405; the fragment of SEQ ID NO:29 from about nucleotide 35 to about nucleotide 79; the fragment of SEQ ID NO:30 from about nucleotide 206 to about nucleotide 250; the fragment of SEQ ID NO:31 from about nucleotide 71 to about nucleotide 115; the fragment of SEQ ID NO:32 from about nucleotide 161 to about nucleotide 205; the fragment of SEQ ID NO:33 from about nucleotide 364 to about nucleotide 408; and the fragment of SEQ ID NO:34 from about nucleotide 18 to about nucleotide 62. The polypeptides encoded by the specified fragments of SEQ ID NO:20-30 and SEQ ID NO:32-34 are useful, for example, as immunogenic peptides.

The columns of Table 4 show descriptions of the tissues used to construct the cDNA libraries from which cDNA clones encoding MTRP were isolated. Column 1 references the nucleotide SEQ ID NOs, column 2 shows the cDNA libraries from which these clones were isolated, and column 3 shows the tissue origins and other descriptive information relevant to the cDNA libraries in column 2.

The invention also encompasses MTRP variants. A preferred MTRP variant is one which has at least about 80%, or alternatively at least about 90%, or even at least about 95% amino acid sequence identity to the MTRP amino acid sequence, and which contains at least one functional or structural characteristic of MTRP.

The invention also encompasses polynucleotides which encode MTRP. In a particular embodiment, the invention encompasses a polynucleotide sequence comprising a sequence selected from the group consisting of SEQ ID NO:18-34, which encodes MTRP.

The invention also encompasses a variant of a polynucleotide sequence encoding MTRP. In particular, such a variant polynucleotide sequence will have at least about 75%, or alternatively at

least about 85%, or even at least about 95% polynucleotide sequence identity to the polynucleotide sequence encoding MTRP. A particular aspect of the invention encompasses a variant of a polynucleotide sequence comprising a sequence selected from the group consisting of SEQ ID NO:18-34 which has at least about 75%, or alternatively at least about 85%, or even at least about 5 95% polynucleotide sequence identity to a nucleic acid sequence selected from the group consisting of SEQ ID NO:18-34. Any one of the polynucleotide variants described above can encode an amino acid sequence which contains at least one functional or structural characteristic of MTRP.

It will be appreciated by those skilled in the art that as a result of the degeneracy of the genetic code, a multitude of polynucleotide sequences encoding MTRP, some bearing minimal 10 similarity to the polynucleotide sequences of any known and naturally occurring gene, may be produced. Thus, the invention contemplates each and every possible variation of polynucleotide sequence that could be made by selecting combinations based on possible codon choices. These combinations are made in accordance with the standard triplet genetic code as applied to the polynucleotide sequence of naturally occurring MTRP, and all such variations are to be considered as 15 being specifically disclosed.

Although nucleotide sequences which encode MTRP and its variants are generally capable of hybridizing to the nucleotide sequence of the naturally occurring MTRP under appropriately selected conditions of stringency, it may be advantageous to produce nucleotide sequences encoding MTRP or its derivatives possessing a substantially different codon usage, e.g., inclusion of non-naturally 20 occurring codons. Codons may be selected to increase the rate at which expression of the peptide occurs in a particular prokaryotic or eukaryotic host in accordance with the frequency with which particular codons are utilized by the host. Other reasons for substantially altering the nucleotide sequence encoding MTRP and its derivatives without altering the encoded amino acid sequences include the production of RNA transcripts having more desirable properties, such as a greater 25 half-life, than transcripts produced from the naturally occurring sequence.

The invention also encompasses production of DNA sequences which encode MTRP and MTRP derivatives, or fragments thereof, entirely by synthetic chemistry. After production, the synthetic sequence may be inserted into any of the many available expression vectors and cell systems using reagents well known in the art. Moreover, synthetic chemistry may be used to introduce 30 mutations into a sequence encoding MTRP or any fragment thereof.

Also encompassed by the invention are polynucleotide sequences that are capable of hybridizing to the claimed polynucleotide sequences, and, in particular, to those shown in SEQ ID NO:18-34 and fragments thereof under various conditions of stringency. (See, e.g., Wahl, G.M. and S.L. Berger (1987) *Methods Enzymol.* 152:399-407; Kimmel, A.R. (1987) *Methods Enzymol.*

152:507-511.) Hybridization conditions, including annealing and wash conditions, are described in "Definitions."

Methods for DNA sequencing are well known in the art and may be used to practice any of the embodiments of the invention. The methods may employ such enzymes as the Klenow fragment of DNA polymerase I, SEQUENASE (US Biochemical, Cleveland OH), Taq polymerase (Perkin-Elmer), thermostable T7 polymerase (Amersham Pharmacia Biotech, Piscataway NJ), or combinations of polymerases and proofreading exonucleases such as those found in the ELONGASE amplification system (Life Technologies, Gaithersburg MD). Preferably, sequence preparation is automated with machines such as the MICROLAB 2200 liquid transfer system (Hamilton, Reno NV), PTC200 thermal cycler (MJ Research, Watertown MA) and ABI CATALYST 800 thermal cycler (Perkin-Elmer). Sequencing is then carried out using either the ABI 373 or 377 DNA sequencing system (Perkin-Elmer), the MEGABACE 1000 DNA sequencing system (Molecular Dynamics, Sunnyvale CA), or other systems known in the art. The resulting sequences are analyzed using a variety of algorithms which are well known in the art. (See, e.g., Ausubel, F.M. (1997) Short Protocols in Molecular Biology, John Wiley & Sons, New York NY, unit 7.7; Meyers, R.A. (1995) Molecular Biology and Biotechnology, Wiley VCH, New York NY, pp. 856-853.)

The nucleic acid sequences encoding MTRP may be extended utilizing a partial nucleotide sequence and employing various PCR-based methods known in the art to detect upstream sequences, such as promoters and regulatory elements. For example, one method which may be employed, restriction-site PCR, uses universal and nested primers to amplify unknown sequence from genomic DNA within a cloning vector. (See, e.g., Sarkar, G. (1993) *PCR Methods Applic.* 2:318-322.) Another method, inverse PCR, uses primers that extend in divergent directions to amplify unknown sequence from a circularized template. The template is derived from restriction fragments comprising a known genomic locus and surrounding sequences. (See, e.g., Triglia, T. et al. (1988) *Nucleic Acids Res.* 16:8186.) A third method, capture PCR, involves PCR amplification of DNA fragments adjacent to known sequences in human and yeast artificial chromosome DNA. (See, e.g., Lagerstrom, M. et al. (1991) *PCR Methods Applic.* 1:111-119.) In this method, multiple restriction enzyme digestions and ligations may be used to insert an engineered double-stranded sequence into a region of unknown sequence before performing PCR. Other methods which may be used to retrieve unknown sequences are known in the art. (See, e.g., Parker, J.D. et al. (1991) *Nucleic Acids Res.* 19:3055-3060.) Additionally, one may use PCR, nested primers, and PROMOTERFINDER libraries (Clontech, Palo Alto CA) to walk genomic DNA. This procedure avoids the need to screen libraries and is useful in finding intron/exon junctions. For all PCR-based methods, primers may be designed using commercially available software, such as OLIGO 4.06 Primer Analysis software (National

Biosciences, Plymouth MN) or another appropriate program, to be about 22 to 30 nucleotides in length, to have a GC content of about 50% or more, and to anneal to the template at temperatures of about 68°C to 72°C.

When screening for full-length cDNAs, it is preferable to use libraries that have been
5 size-selected to include larger cDNAs. In addition, random-primed libraries, which often include sequences containing the 5' regions of genes, are preferable for situations in which an oligo d(T) library does not yield a full-length cDNA. Genomic libraries may be useful for extension of sequence into 5' non-transcribed regulatory regions.

Capillary electrophoresis systems which are commercially available may be used to analyze
10 the size or confirm the nucleotide sequence of sequencing or PCR products. In particular, capillary sequencing may employ flowable polymers for electrophoretic separation, four different nucleotide-specific, laser-stimulated fluorescent dyes, and a charge coupled device camera for detection of the emitted wavelengths. Output/light intensity may be converted to electrical signal using appropriate software (e.g., GENOTYPER and SEQUENCE NAVIGATOR, Perkin-Elmer), and the entire process
15 from loading of samples to computer analysis and electronic data display may be computer controlled. Capillary electrophoresis is especially preferable for sequencing small DNA fragments which may be present in limited amounts in a particular sample.

In another embodiment of the invention, polynucleotide sequences or fragments thereof which encode MTRP may be cloned in recombinant DNA molecules that direct expression of MTRP,
20 or fragments or functional equivalents thereof, in appropriate host cells. Due to the inherent degeneracy of the genetic code, other DNA sequences which encode substantially the same or a functionally equivalent amino acid sequence may be produced and used to express MTRP.

The nucleotide sequences of the present invention can be engineered using methods generally known in the art in order to alter MTRP-encoding sequences for a variety of purposes including, but
25 not limited to, modification of the cloning, processing, and/or expression of the gene product. DNA shuffling by random fragmentation and PCR reassembly of gene fragments and synthetic oligonucleotides may be used to engineer the nucleotide sequences. For example, oligonucleotide-mediated site-directed mutagenesis may be used to introduce mutations that create new restriction sites, alter glycosylation patterns, change codon preference, produce splice variants, and so forth.

30 In another embodiment, sequences encoding MTRP may be synthesized, in whole or in part, using chemical methods well known in the art. (See, e.g., Caruthers, M.H. et al. (1980) Nucleic Acids Symp. Ser. 7:215-223; and Horn, T. et al. (1980) Nucleic Acids Symp. Ser. 7:225-232.) Alternatively, MTRP itself or a fragment thereof may be synthesized using chemical methods. For example, peptide synthesis can be performed using various solid-phase techniques. (See, e.g.,

Roberge, J.Y. et al. (1995) Science 269:202-204.) Automated synthesis may be achieved using the ABI 431A peptide synthesizer (Perkin-Elmer). Additionally, the amino acid sequence of MTRP, or any part thereof, may be altered during direct synthesis and/or combined with sequences from other proteins, or any part thereof, to produce a variant polypeptide.

5 The peptide may be substantially purified by preparative high performance liquid chromatography. (See, e.g., Chiez, R.M. and F.Z. Regnier (1990) Methods Enzymol. 182:392-421.) The composition of the synthetic peptides may be confirmed by amino acid analysis or by sequencing. (See, e.g., Creighton, T. (1984) Proteins, Structures and Molecular Properties, WH Freeman, New York NY.)

10 In order to express a biologically active MTRP, the nucleotide sequences encoding MTRP or derivatives thereof may be inserted into an appropriate expression vector, i.e., a vector which contains the necessary elements for transcriptional and translational control of the inserted coding sequence in a suitable host. These elements include regulatory sequences, such as enhancers, constitutive and inducible promoters, and 5' and 3' untranslated regions in the vector and in polynucleotide sequences
15 encoding MTRP. Such elements may vary in their strength and specificity. Specific initiation signals may also be used to achieve more efficient translation of sequences encoding MTRP. Such signals include the ATG initiation codon and adjacent sequences, e.g. the Kozak sequence. In cases where sequences encoding MTRP and its initiation codon and upstream regulatory sequences are inserted into the appropriate expression vector, no additional transcriptional or translational control signals
20 may be needed. However, in cases where only coding sequence, or a fragment thereof, is inserted, exogenous translational control signals including an in-frame ATG initiation codon should be provided by the vector. Exogenous translational elements and initiation codons may be of various origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of enhancers appropriate for the particular host cell system used. (See, e.g., Scharf, D. et al. (1994) Results Probl. Cell Differ. 20:125-162.)

25 Methods which are well known to those skilled in the art may be used to construct expression vectors containing sequences encoding MTRP and appropriate transcriptional and translational control elements. These methods include in vitro recombinant DNA techniques, synthetic techniques, and in vivo genetic recombination. (See, e.g., Sambrook, J. et al. (1989) Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Press, Plainview NY, ch. 4, 8, and 16-17; Ausubel, F.M. et al. (1995) Current Protocols in Molecular Biology, John Wiley & Sons, New York NY, ch. 9, 13, and 16.)

A variety of expression vector/host systems may be utilized to contain and express sequences encoding MTRP. These include, but are not limited to, microorganisms such as bacteria transformed

with recombinant bacteriophage, plasmid, or cosmid DNA expression vectors; yeast transformed with yeast expression vectors; insect cell systems infected with viral expression vectors (e.g., baculovirus); plant cell systems transformed with viral expression vectors (e.g., cauliflower mosaic virus, CaMV, or tobacco mosaic virus, TMV) or with bacterial expression vectors (e.g., Ti or pBR322 plasmids); or
5 animal cell systems. The invention is not limited by the host cell employed.

In bacterial systems, a number of cloning and expression vectors may be selected depending upon the use intended for polynucleotide sequences encoding MTRP. For example, routine cloning, subcloning, and propagation of polynucleotide sequences encoding MTRP can be achieved using a multifunctional *E. coli* vector such as PBLUESCRIPT (Stratagene, La Jolla CA) or PSPT1
10 plasmid (Life Technologies). Ligation of sequences encoding MTRP into the vector's multiple cloning site disrupts the *lacZ* gene, allowing a colorimetric screening procedure for identification of transformed bacteria containing recombinant molecules. In addition, these vectors may be useful for *in vitro* transcription, dideoxy sequencing, single strand rescue with helper phage, and creation of nested deletions in the cloned sequence. (See, e.g., Van Heeke, G. and S.M. Schuster (1989) J. Biol.
15 Chem. 264:5503-5509.) When large quantities of MTRP are needed, e.g. for the production of antibodies, vectors which direct high level expression of MTRP may be used. For example, vectors containing the strong, inducible T5 or T7 bacteriophage promoter may be used.

Yeast expression systems may be used for production of MTRP. A number of vectors containing constitutive or inducible promoters, such as alpha factor, alcohol oxidase, and PGH
20 promoters, may be used in the yeast *Saccharomyces cerevisiae* or *Pichia pastoris*. In addition, such vectors direct either the secretion or intracellular retention of expressed proteins and enable integration of foreign sequences into the host genome for stable propagation. (See, e.g., Ausubel, 1995, *supra*; Bitter, G.A. et al. (1987) Methods Enzymol. 153:516-544; and Scorer, C.A. et al. (1994) Bio/Technology 12:181-184.)

25 Plant systems may also be used for expression of MTRP. Transcription of sequences encoding MTRP may be driven viral promoters, e.g., the 35S and 19S promoters of CaMV used alone or in combination with the omega leader sequence from TMV (Takamatsu, N. (1987) EMBO J. 6:307-311). Alternatively, plant promoters such as the small subunit of RUBISCO or heat shock promoters may be used. (See, e.g., Coruzzi, G. et al. (1984) EMBO J. 3:1671-1680; Broglie, R. et al. (1984) Science 224:838-843; and Winter, J. et al. (1991) Results Probl. Cell Differ. 17:85-105.)
30 These constructs can be introduced into plant cells by direct DNA transformation or pathogen-mediated transfection. (See, e.g., The McGraw Hill Yearbook of Science and Technology (1992) McGraw Hill, New York NY, pp. 191-196.)

In mammalian cells, a number of viral-based expression systems may be utilized. In cases

where an adenovirus is used as an expression vector, sequences encoding MTRP may be ligated into an adenovirus transcription/translation complex consisting of the late promoter and tripartite leader sequence. Insertion in a non-essential E1 or E3 region of the viral genome may be used to obtain infective virus which expresses MTRP in host cells. (See, e.g., Logan, J. and T. Shenk (1984) Proc. Natl. Acad. Sci. USA 81:3655-3659.) In addition, transcription enhancers, such as the Rous sarcoma virus (RSV) enhancer, may be used to increase expression in mammalian host cells. SV40 or EBV-based vectors may also be used for high-level protein expression.

Human artificial chromosomes (HACs) may also be employed to deliver larger fragments of DNA than can be contained in and expressed from a plasmid. HACs of about 6 kb to 10 Mb are constructed and delivered via conventional delivery methods (liposomes, polycationic amino polymers, or vesicles) for therapeutic purposes. (See, e.g., Harrington, J.J. et al. (1997) Nat. Genet. 15:345-355.)

For long term production of recombinant proteins in mammalian systems, stable expression of MTRP in cell lines is preferred. For example, sequences encoding MTRP can be transformed into cell lines using expression vectors which may contain viral origins of replication and/or endogenous expression elements and a selectable marker gene on the same or on a separate vector. Following the introduction of the vector, cells may be allowed to grow for about 1 to 2 days in enriched media before being switched to selective media. The purpose of the selectable marker is to confer resistance to a selective agent, and its presence allows growth and recovery of cells which successfully express the introduced sequences. Resistant clones of stably transformed cells may be propagated using tissue culture techniques appropriate to the cell type.

Any number of selection systems may be used to recover transformed cell lines. These include, but are not limited to, the herpes simplex virus thymidine kinase and adenine phosphoribosyltransferase genes, for use in *tk*⁻ and *apv*⁻ cells, respectively. (See, e.g., Wigler, M. et al. (1977) Cell 11:223-232; Lowy, I. et al. (1980) Cell 22:817-823.) Also, antimetabolite, antibiotic, or herbicide resistance can be used as the basis for selection. For example, *dhfr* confers resistance to methotrexate; *neo* confers resistance to the aminoglycosides neomycin and G-418; and *als* and *pat* confer resistance to chlorsulfuron and phosphinotricin acetyltransferase, respectively. (See, e.g., Wigler, M. et al. (1980) Proc. Natl. Acad. Sci. USA 77:3567-3570; Colbere-Garapin, F. et al. (1981) J. Mol. Biol. 150:1-14.) Additional selectable genes have been described, e.g., *trpB* and *hisD*, which alter cellular requirements for metabolites. (See, e.g., Hartman, S.C. and R.C. Mulligan (1988) Proc. Natl. Acad. Sci. USA 85:8047-8051.) Visible markers, e.g., anthocyanins, green fluorescent proteins (GFP; Clontech), β glucuronidase and its substrate β -glucuronide, or luciferase and its substrate luciferin may be used. These markers can be used not only to identify transformants, but also to

quantify the amount of transient or stable protein expression attributable to a specific vector system.
(See, e.g., Rhodes, C.A. (1995) *Methods Mol. Biol.* 55:121-131.)

Although the presence/absence of marker gene expression suggests that the gene of interest is also present, the presence and expression of the gene may need to be confirmed. For example, if the
5 sequence encoding MTRP is inserted within a marker gene sequence, transformed cells containing sequences encoding MTRP can be identified by the absence of marker gene function. Alternatively, a marker gene can be placed in tandem with a sequence encoding MTRP under the control of a single promoter. Expression of the marker gene in response to induction or selection usually indicates expression of the tandem gene as well.

10 In general, host cells that contain the nucleic acid sequence encoding MTRP and that express MTRP may be identified by a variety of procedures known to those of skill in the art. These procedures include, but are not limited to, DNA-DNA or DNA-RNA hybridizations, PCR amplification, and protein bioassay or immunoassay techniques which include membrane, solution, or chip based technologies for the detection and/or quantification of nucleic acid or protein sequences.

15 Immunological methods for detecting and measuring the expression of MTRP using either specific polyclonal or monoclonal antibodies are known in the art. Examples of such techniques include enzyme-linked immunosorbent assays (ELISAs), radioimmunoassays (RIAs), and fluorescence activated cell sorting (FACS). A two-site, monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two non-interfering epitopes on MTRP is preferred, but a
20 competitive binding assay may be employed. These and other assays are well known in the art. (See, e.g., Hampton, R. et al. (1990) Serological Methods, a Laboratory Manual, APS Press, St. Paul MN, Sect. IV; Coligan, J.E. et al. (1997) Current Protocols in Immunology, Greene Pub. Associates and Wiley-Interscience, New York NY; and Pound, J.D. (1998) Immunochemical Protocols, Humana Press, Totowa NJ.)

25 A wide variety of labels and conjugation techniques are known by those skilled in the art and may be used in various nucleic acid and amino acid assays. Means for producing labeled hybridization or PCR probes for detecting sequences related to polynucleotides encoding MTRP include oligolabeling, nick translation, end-labeling, or PCR amplification using a labeled nucleotide. Alternatively, the sequences encoding MTRP, or any fragments thereof, may be cloned into a vector
30 for the production of an mRNA probe. Such vectors are known in the art, are commercially available, and may be used to synthesize RNA probes *in vitro* by addition of an appropriate RNA polymerase such as T7, T3, or SP6 and labeled nucleotides. These procedures may be conducted using a variety of commercially available kits, such as those provided by Amersham Pharmacia Biotech, Promega (Madison WI), and US Biochemical. Suitable reporter molecules or labels which may be used for

ease of detection include radionuclides, enzymes, fluorescent, chemiluminescent, or chromogenic agents, as well as substrates, cofactors, inhibitors, magnetic particles, and the like.

Host cells transformed with nucleotide sequences encoding MTRP may be cultured under conditions suitable for the expression and recovery of the protein from cell culture. The protein
5 produced by a transformed cell may be secreted or retained intracellularly depending on the sequence and/or the vector used. As will be understood by those of skill in the art, expression vectors containing polynucleotides which encode MTRP may be designed to contain signal sequences which direct secretion of MTRP through a prokaryotic or eukaryotic cell membrane.

In addition, a host cell strain may be chosen for its ability to modulate expression of the
10 inserted sequences or to process the expressed protein in the desired fashion. Such modifications of the polypeptide include, but are not limited to, acetylation, carboxylation, glycosylation, phosphorylation, lipidation, and acylation. Post-translational processing which cleaves a "prepro" or "pro" form of the protein may also be used to specify protein targeting, folding, and/or activity. Different host cells which have specific cellular machinery and characteristic mechanisms for
15 post-translational activities (e.g., CHO, HeLa, MDCK, HEK293, and WI38) are available from the American Type Culture Collection (ATCC, Manassas VA) and may be chosen to ensure the correct modification and processing of the foreign protein.

In another embodiment of the invention, natural, modified, or recombinant nucleic acid sequences encoding MTRP may be ligated to a heterologous sequence resulting in translation of a
20 fusion protein in any of the aforementioned host systems. For example, a chimeric MTRP protein containing a heterologous moiety that can be recognized by a commercially available antibody may facilitate the screening of peptide libraries for inhibitors of MTRP activity. Heterologous protein and peptide moieties may also facilitate purification of fusion proteins using commercially available affinity matrices. Such moieties include, but are not limited to, glutathione S-transferase (GST),
25 maltose binding protein (MBP), thioredoxin (Trx), calmodulin binding peptide (CBP), 6-His, FLAG, *c-myc*, and hemagglutinin (HA). GST, MBP, Trx, CBP, and 6-His enable purification of their cognate fusion proteins on immobilized glutathione, maltose, phenylarsine oxide, calmodulin, and metal-chelate resins, respectively. FLAG, *c-myc*, and hemagglutinin (HA) enable immunoaffinity
purification of fusion proteins using commercially available monoclonal and polyclonal antibodies
30 that specifically recognize these epitope tags. A fusion protein may also be engineered to contain a proteolytic cleavage site located between the MTRP encoding sequence and the heterologous protein sequence, so that MTRP may be cleaved away from the heterologous moiety following purification. Methods for fusion protein expression and purification are discussed in Ausubel (1995, *supra*, ch. 10). A variety of commercially available kits may also be used to facilitate expression and purification of

fusion proteins.

In a further embodiment of the invention, synthesis of radiolabeled MTRP may be achieved in vitro using the TNT rabbit reticulocyte lysate or wheat germ extract system (Promega). These systems couple transcription and translation of protein-coding sequences operably associated with the T7, T3, or SP6 promoters. Translation takes place in the presence of a radiolabeled amino acid precursor, for example, ³⁵S-methionine.

Fragments of MTRP may be produced not only by recombinant means, but also by direct peptide synthesis using solid-phase techniques. (See, e.g., Creighton, supra, pp. 55-60.) Protein synthesis may be performed by manual techniques or by automation. Automated synthesis may be achieved, for example, using the ABI 431A peptide synthesizer (Perkin-Elmer). Various fragments of MTRP may be synthesized separately and then combined to produce the full length molecule.

THERAPEUTICS

Chemical and structural similarity, e.g., in the context of sequences and motifs, exists between regions of MTRP and membrane transport proteins, including amino acid transporters, ABC transporters, nucleotide-sugar transporters, transmembrane carrier proteins, and ATP-dependent transporter proteins. In addition, the expression of MTRP is closely associated with nervous, reproductive, and gastrointestinal tissues; cancer and other cell proliferative conditions; and with inflammation and the immune response. Therefore, MTRP appears to play a role in membrane transport disorders; immune/inflammatory disorders; and cell proliferative disorders including cancer.

In the treatment of disorders associated with increased MTRP expression or activity, it is desirable to decrease the expression or activity of MTRP. In the treatment of disorders associated with decreased MTRP expression or activity, it is desirable to increase the expression or activity of MTRP.

Therefore, in one embodiment, MTRP or a fragment or derivative thereof may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of MTRP. Examples of such disorders include, but are not limited to, a membrane transport disorder such as cystinuria, dibasicaminoaciduria, hypercystinuria, lysinuria, hartnup disease, tryptophan malabsorption, methionine malabsorption, histidinuria, iminoglycinuria, dicarboxylicaminoaciduria, cystinosis, renal glycosuria, glucose-galactose malabsorption, familial hypercholesterolemia, hypouricemia, familial hypophosphatemic rickets, congenital chloridorrhea, cystic fibrosis, familial goiter, distal renal tubular acidosis, Menkes' disease, lethal diarrhea, nephrogenic diabetes insipidus, juvenile pernicious anemia, folate malabsorption, adrenoleukodystrophy, hereditary myoglobinuria, Zellweger syndrome, hyperinsulinemic hypoglycemia, akinesia, amyotrophic lateral sclerosis, ataxia telangiectasia, cystic fibrosis, Becker's muscular dystrophy, Bell's palsy, Charcot-Marie Tooth disease, diabetes mellitus, diabetes insipidus,

- diabetic neuropathy, Duchenne muscular dystrophy, hyperkalemic periodic paralysis, normokalemic periodic paralysis, Parkinson's disease, malignant hyperthermia, multidrug resistance, myasthenia gravis, myotonic dystrophy, catatonia, tardive dyskinesia, dystonias, peripheral neuropathy, cerebral neoplasms, and prostate cancer; a cardiac disorder associated with transport such as angina,
- 5 bradyarrhythmia, tachyarrhythmia, hypertension, Long QT syndrome, myocarditis, cardiomyopathy, nemaline myopathy, centronuclear myopathy, lipid myopathy, mitochondrial myopathy, thyrotoxic myopathy, ethanol myopathy, dermatomyositis, inclusion body myositis, infectious myositis, and polymyositis; a neurological disorder associated with transport such as Alzheimer's disease, amnesia, bipolar disorder, dementia, depression, epilepsy, Tourette's disorder, paranoid psychoses, and
- 10 schizophrenia; and an other disorder associated with transport such as neurofibromatosis, postherpetic neuralgia, trigeminal neuropathy, sarcoidosis, sickle cell anemia, Wilson's disease, cataracts, infertility, pulmonary artery stenosis, sensorineural autosomal deafness, hyperglycemia, hypoglycemia, Grave's disease, goiter, Cushing's disease, Addison's disease, glucose-galactose malabsorption syndrome, and hypercholesterolemia; an immune/inflammatory disorder such as
- 15 acquired immunodeficiency syndrome (AIDS), Addison's disease, adult respiratory distress syndrome, allergies, ankylosing spondylitis, amyloidosis, anemia, asthma, atherosclerosis, autoimmune hemolytic anemia, autoimmune thyroiditis, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), bronchitis, cholecystitis, contact dermatitis, Crohn's disease, atopic dermatitis, dermatomyositis, diabetes mellitus, emphysema, episodic lymphopenia
- 20 with lymphocytotoxins, erythroblastosis fetalis, erythema nodosum, atrophic gastritis, glomerulonephritis, Goodpasture's syndrome, gout, Graves' disease, Hashimoto's thyroiditis, hypereosinophilia, irritable bowel syndrome, multiple sclerosis, myasthenia gravis, myocardial or pericardial inflammation, osteoarthritis, osteoporosis, pancreatitis, polymyositis, psoriasis, Reiter's syndrome, rheumatoid arthritis, scleroderma, Sjögren's syndrome, systemic anaphylaxis, systemic
- 25 lupus erythematosus, systemic sclerosis, thrombocytopenic purpura, ulcerative colitis, uveitis, Werner syndrome, complications of cancer, hemodialysis, and extracorporeal circulation; a viral, bacterial, fungal, parasitic, protozoal, or helminthic infection; and trauma; a cell proliferative disorder such as actinic keratosis, arteriosclerosis, atherosclerosis, bursitis, cirrhosis, hepatitis, mixed connective tissue disease (MCTD), myelofibrosis, paroxysmal nocturnal hemoglobinuria, polycythemia vera, psoriasis,
- 30 primary thrombocythemia; and a cancer including adenocarcinoma, leukemia, lymphoma, melanoma, myeloma, sarcoma, teratocarcinoma; and, in particular, a cancer of the adrenal gland, bladder, bone, bone marrow, brain, breast, cervix, gall bladder, ganglia, gastrointestinal tract, heart, kidney, liver, lung, muscle, ovary, pancreas, parathyroid, penis, prostate, salivary glands, skin, spleen, testis, thymus, thyroid, and uterus.

In another embodiment, a vector capable of expressing MTRP or a fragment or derivative thereof may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of MTRP including, but not limited to, those described above.

In a further embodiment, a pharmaceutical composition comprising a substantially purified MTRP in conjunction with a suitable pharmaceutical carrier may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of MTRP including, but not limited to, those provided above.

In still another embodiment, an agonist which modulates the activity of MTRP may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of MTRP including, but not limited to, those listed above.

In a further embodiment, an antagonist of MTRP may be administered to a subject to treat or prevent a disorder associated with increased expression or activity of MTRP. Examples of such disorders include, but are not limited to, those membrane transport disorders; immune/inflammatory disorders; and cell proliferative disorders including cancer described above. In one aspect, an antibody which specifically binds MTRP may be used directly as an antagonist or indirectly as a targeting or delivery mechanism for bringing a pharmaceutical agent to cells or tissues which express MTRP.

In an additional embodiment, a vector expressing the complement of the polynucleotide encoding MTRP may be administered to a subject to treat or prevent a disorder associated with increased expression or activity of MTRP including, but not limited to, those described above.

In other embodiments, any of the proteins, antagonists, antibodies, agonists, complementary sequences, or vectors of the invention may be administered in combination with other appropriate therapeutic agents. Selection of the appropriate agents for use in combination therapy may be made by one of ordinary skill in the art, according to conventional pharmaceutical principles. The combination of therapeutic agents may act synergistically to effect the treatment or prevention of the various disorders described above. Using this approach, one may be able to achieve therapeutic efficacy with lower dosages of each agent, thus reducing the potential for adverse side effects.

An antagonist of MTRP may be produced using methods which are generally known in the art. In particular, purified MTRP may be used to produce antibodies or to screen libraries of pharmaceutical agents to identify those which specifically bind MTRP. Antibodies to MTRP may also be generated using methods that are well known in the art. Such antibodies may include, but are not limited to, polyclonal, monoclonal, chimeric, and single chain antibodies, Fab fragments, and fragments produced by a Fab expression library. Neutralizing antibodies (i.e., those which inhibit dimer formation) are generally preferred for therapeutic use.

For the production of antibodies, various hosts including goats, rabbits, rats, mice, humans, and others may be immunized by injection with MTRP or with any fragment or oligopeptide thereof which has immunogenic properties. Depending on the host species, various adjuvants may be used to increase immunological response. Such adjuvants include, but are not limited to, Freund's, mineral
5 gels such as aluminum hydroxide, and surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, KLH, and dinitrophenol. Among adjuvants used in humans, BCG (bacilli Calmette-Guerin) and Corynebacterium parvum are especially preferable.

It is preferred that the oligopeptides, peptides, or fragments used to induce antibodies to MTRP have an amino acid sequence consisting of at least about 5 amino acids, and generally will
10 consist of at least about 10 amino acids. It is also preferable that these oligopeptides, peptides, or fragments are identical to a portion of the amino acid sequence of the natural protein and contain the entire amino acid sequence of a small, naturally occurring molecule. Short stretches of MTRP amino acids may be fused with those of another protein, such as KLH, and antibodies to the chimeric molecule may be produced.

15 Monoclonal antibodies to MTRP may be prepared using any technique which provides for the production of antibody molecules by continuous cell lines in culture. These include, but are not limited to, the hybridoma technique, the human B-cell hybridoma technique, and the EBV-hybridoma technique. (See, e.g., Kohler, G. et al. (1975) Nature 256:495-497; Kozbor, D. et al. (1985) J. Immunol. Methods 81:31-42; Cote, R.J. et al. (1983) Proc. Natl. Acad. Sci. USA 80:2026-2030; and
20 Cole, S.P. et al. (1984) Mol. Cell Biol. 62:109-120.)

In addition, techniques developed for the production of "chimeric antibodies," such as the splicing of mouse antibody genes to human antibody genes to obtain a molecule with appropriate antigen specificity and biological activity, can be used. (See, e.g., Morrison, S.L. et al. (1984) Proc. Natl. Acad. Sci. USA 81:6851-6855; Neuberger, M.S. et al. (1984) Nature 312:604-608; and Takeda,
25 S. et al. (1985) Nature 314:452-454.) Alternatively, techniques described for the production of single chain antibodies may be adapted, using methods known in the art, to produce MTRP-specific single chain antibodies. Antibodies with related specificity, but of distinct idiotypic composition, may be generated by chain shuffling from random combinatorial immunoglobulin libraries. (See, e.g., Burton, D.R. (1991) Proc. Natl. Acad. Sci. USA 88:10134-10137.)

30 Antibodies may also be produced by inducing in vivo production in the lymphocyte population or by screening immunoglobulin libraries or panels of highly specific binding reagents as disclosed in the literature. (See, e.g., Orlandi, R. et al. (1989) Proc. Natl. Acad. Sci. USA 86:3833-3837; Winter, G. et al. (1991) Nature 349:293-299.)

Antibody fragments which contain specific binding sites for MTRP may also be generated.

For example, such fragments include, but are not limited to, $F(ab')_2$ fragments produced by pepsin digestion of the antibody molecule and Fab fragments generated by reducing the disulfide bridges of the $F(ab')_2$ fragments. Alternatively, Fab expression libraries may be constructed to allow rapid and easy identification of monoclonal Fab fragments with the desired specificity. (See, e.g., Huse, W.D. et al. (1989) Science 246:1275-1281.)

Various immunoassays may be used for screening to identify antibodies having the desired specificity. Numerous protocols for competitive binding or immunoradiometric assays using either polyclonal or monoclonal antibodies with established specificities are well known in the art. Such immunoassays typically involve the measurement of complex formation between MTRP and its specific antibody. A two-site, monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two non-interfering MTRP epitopes is generally used, but a competitive binding assay may also be employed (Pound, supra).

Various methods such as Scatchard analysis in conjunction with radioimmunoassay techniques may be used to assess the affinity of antibodies for MTRP. Affinity is expressed as an association constant, K_a , which is defined as the molar concentration of MTRP-antibody complex divided by the molar concentrations of free antigen and free antibody under equilibrium conditions. The K_a determined for a preparation of polyclonal antibodies, which are heterogeneous in their affinities for multiple MTRP epitopes, represents the average affinity, or avidity, of the antibodies for MTRP. The K_a determined for a preparation of monoclonal antibodies, which are monospecific for a particular MTRP epitope, represents a true measure of affinity. High-affinity antibody preparations with K_a ranging from about 10^9 to 10^{12} L/mole are preferred for use in immunoassays in which the MTRP-antibody complex must withstand rigorous manipulations. Low-affinity antibody preparations with K_a ranging from about 10^6 to 10^7 L/mole are preferred for use in immunopurification and similar procedures which ultimately require dissociation of MTRP, preferably in active form, from the antibody (Catty, D. (1988) Antibodies, Volume I: A Practical Approach, IRL Press, Washington, DC; Liddell, J.E. and Cryer, A. (1991) A Practical Guide to Monoclonal Antibodies, John Wiley & Sons, New York NY).

The titer and avidity of polyclonal antibody preparations may be further evaluated to determine the quality and suitability of such preparations for certain downstream applications. For example, a polyclonal antibody preparation containing at least 1-2 mg specific antibody/ml, preferably 5-10 mg specific antibody/ml, is generally employed in procedures requiring precipitation of MTRP-antibody complexes. Procedures for evaluating antibody specificity, titer, and avidity, and guidelines for antibody quality and usage in various applications, are generally available. (See, e.g., Catty, supra, and Coligan et al. supra.)

In another embodiment of the invention, the polynucleotides encoding MTRP, or any fragment or complement thereof, may be used for therapeutic purposes. In one aspect, the complement of the polynucleotide encoding MTRP may be used in situations in which it would be desirable to block the transcription of the mRNA. In particular, cells may be transformed with
5 sequences complementary to polynucleotides encoding MTRP. Thus, complementary molecules or fragments may be used to modulate MTRP activity, or to achieve regulation of gene function. Such technology is now well known in the art, and sense or antisense oligonucleotides or larger fragments can be designed from various locations along the coding or control regions of sequences encoding MTRP.

10 Expression vectors derived from retroviruses, adenoviruses, or herpes or vaccinia viruses, or from various bacterial plasmids, may be used for delivery of nucleotide sequences to the targeted organ, tissue, or cell population. Methods which are well known to those skilled in the art can be used to construct vectors to express nucleic acid sequences complementary to the polynucleotides encoding MTRP. (See, e.g., Sambrook, supra; Ausubel, 1995, supra.)

15 Genes encoding MTRP can be turned off by transforming a cell or tissue with expression vectors which express high levels of a polynucleotide, or fragment thereof, encoding MTRP. Such constructs may be used to introduce untranslatable sense or antisense sequences into a cell. Even in the absence of integration into the DNA, such vectors may continue to transcribe RNA molecules until they are disabled by endogenous nucleases. Transient expression may last for a month or more
20 with a non-replicating vector, and may last even longer if appropriate replication elements are part of the vector system.

As mentioned above, modifications of gene expression can be obtained by designing complementary sequences or antisense molecules (DNA, RNA, or PNA) to the control, 5', or regulatory regions of the gene encoding MTRP. Oligonucleotides derived from the transcription
25 initiation site, e.g., between about positions -10 and +10 from the start site, may be employed. Similarly, inhibition can be achieved using triple helix base-pairing methodology. Triple helix pairing is useful because it causes inhibition of the ability of the double helix to open sufficiently for the binding of polymerases, transcription factors, or regulatory molecules. Recent therapeutic advances using triplex DNA have been described in the literature. (See, e.g., Gee, J.E. et al. (1994) in Huber,
30 B.E. and B.I. Carr, Molecular and Immunologic Approaches, Futura Publishing, Mt. Kisco NY, pp. 163-177.) A complementary sequence or antisense molecule may also be designed to block translation of mRNA by preventing the transcript from binding to ribosomes.

Ribozymes, enzymatic RNA molecules, may also be used to catalyze the specific cleavage of RNA. The mechanism of ribozyme action involves sequence-specific hybridization of the ribozyme

molecule to complementary target RNA, followed by endonucleolytic cleavage. For example, engineered hammerhead motif ribozyme molecules may specifically and efficiently catalyze endonucleolytic cleavage of sequences encoding MTRP.

Specific ribozyme cleavage sites within any potential RNA target are initially identified by scanning the target molecule for ribozyme cleavage sites, including the following sequences: GUA, GUU, and GUC. Once identified, short RNA sequences of between 15 and 20 ribonucleotides, corresponding to the region of the target gene containing the cleavage site, may be evaluated for secondary structural features which may render the oligonucleotide inoperable. The suitability of candidate targets may also be evaluated by testing accessibility to hybridization with complementary oligonucleotides using ribonuclease protection assays.

Complementary ribonucleic acid molecules and ribozymes of the invention may be prepared by any method known in the art for the synthesis of nucleic acid molecules. These include techniques for chemically synthesizing oligonucleotides such as solid phase phosphoramidite chemical synthesis. Alternatively, RNA molecules may be generated by in vitro and in vivo transcription of DNA sequences encoding MTRP. Such DNA sequences may be incorporated into a wide variety of vectors with suitable RNA polymerase promoters such as T7 or SP6. Alternatively, these cDNA constructs that synthesize complementary RNA, constitutively or inducibly, can be introduced into cell lines, cells, or tissues.

RNA molecules may be modified to increase intracellular stability and half-life. Possible modifications include, but are not limited to, the addition of flanking sequences at the 5' and/or 3' ends of the molecule, or the use of phosphorothioate or 2' O-methyl rather than phosphodiesterase linkages within the backbone of the molecule. This concept is inherent in the production of PNAs and can be extended in all of these molecules by the inclusion of nontraditional bases such as inosine, queosine, and wybutosine, as well as acetyl-, methyl-, thio-, and similarly modified forms of adenine, cytidine, guanine, thymine, and uridine which are not as easily recognized by endogenous endonucleases.

Many methods for introducing vectors into cells or tissues are available and equally suitable for use in vivo, in vitro, and ex vivo. For ex vivo therapy, vectors may be introduced into stem cells taken from the patient and clonally propagated for autologous transplant back into that same patient. Delivery by transfection, by liposome injections, or by polycationic amino polymers may be achieved using methods which are well known in the art. (See, e.g., Goldman, C.K. et al. (1997) Nat. Biotechnol. 15:462-466.)

Any of the therapeutic methods described above may be applied to any subject in need of such therapy, including, for example, mammals such as humans, dogs, cats, cows, horses, rabbits, and monkeys.

An additional embodiment of the invention relates to the administration of a pharmaceutical or sterile composition, in conjunction with a pharmaceutically acceptable carrier, for any of the therapeutic effects discussed above. Such pharmaceutical compositions may consist of MTRP, antibodies to MTRP, and mimetics, agonists, antagonists, or inhibitors of MTRP. The compositions
5 may be administered alone or in combination with at least one other agent, such as a stabilizing compound, which may be administered in any sterile, biocompatible pharmaceutical carrier including, but not limited to, saline, buffered saline, dextrose, and water. The compositions may be administered to a patient alone, or in combination with other agents, drugs, or hormones.

The pharmaceutical compositions utilized in this invention may be administered by any
10 number of routes including, but not limited to, oral, intravenous, intramuscular, intra-arterial, intramedullary, intrathecal, intraventricular, transdermal, subcutaneous, intraperitoneal, intranasal, enteral, topical, sublingual, or rectal means.

In addition to the active ingredients, these pharmaceutical compositions may contain suitable pharmaceutically-acceptable carriers comprising excipients and auxiliaries which facilitate processing
15 of the active compounds into preparations which can be used pharmaceutically. Further details on techniques for formulation and administration may be found in the latest edition of Remington's Pharmaceutical Sciences (Maack Publishing, Easton PA).

Pharmaceutical compositions for oral administration can be formulated using pharmaceutically acceptable carriers well known in the art in dosages suitable for oral administration.
20 Such carriers enable the pharmaceutical compositions to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions, and the like, for ingestion by the patient.

Pharmaceutical preparations for oral use can be obtained through combining active compounds with solid excipient and processing the resultant mixture of granules (optionally, after grinding) to obtain tablets or dragee cores. Suitable auxiliaries can be added, if desired. Suitable
25 excipients include carbohydrate or protein fillers, such as sugars, including lactose, sucrose, mannitol, and sorbitol; starch from corn, wheat, rice, potato, or other plants; cellulose, such as methyl cellulose, hydroxypropylmethyl-cellulose, or sodium carboxymethylcellulose; gums, including arabic and tragacanth; and proteins, such as gelatin and collagen. If desired, disintegrating or solubilizing agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, and alginic acid or a salt thereof,
30 such as sodium alginate.

Dragee cores may be used in conjunction with suitable coatings, such as concentrated sugar solutions, which may also contain gum arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for product identification or to

characterize the quantity of active compound, i.e., dosage. .

Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a coating, such as glycerol or sorbitol. Push-fit capsules can contain active ingredients mixed with fillers or binders, such as lactose or
5 starches, lubricants, such as talc or magnesium stearate, and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid, or liquid polyethylene glycol with or without stabilizers.

Pharmaceutical formulations suitable for parenteral administration may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hanks' solution, Ringer's
10 solution, or physiologically buffered saline. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils, such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate, triglycerides, or liposomes. Non-lipid polycationic
15 amino polymers may also be used for delivery. Optionally, the suspension may also contain suitable stabilizers or agents to increase the solubility of the compounds and allow for the preparation of highly concentrated solutions.

For topical or nasal administration, penetrants appropriate to the particular barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

20 The pharmaceutical compositions of the present invention may be manufactured in a manner that is known in the art, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping, or lyophilizing processes.

The pharmaceutical composition may be provided as a salt and can be formed with many acids, including but not limited to, hydrochloric, sulfuric, acetic, lactic, tartaric, malic, and succinic
25 acids. Salts tend to be more soluble in aqueous or other protonic solvents than are the corresponding free base forms. In other cases, the preparation may be a lyophilized powder which may contain any or all of the following: 1 mM to 50 mM histidine, 0.1% to 2% sucrose, and 2% to 7% mannitol, at a pH range of 4.5 to 5.5, that is combined with buffer prior to use.

After pharmaceutical compositions have been prepared, they can be placed in an appropriate
30 container and labeled for treatment of an indicated condition. For administration of MTRP, such labeling would include amount, frequency, and method of administration.

Pharmaceutical compositions suitable for use in the invention include compositions wherein the active ingredients are contained in an effective amount to achieve the intended purpose. The determination of an effective dose is well within the capability of those skilled in the art.

For any compound, the therapeutically effective dose can be estimated initially either in cell culture assays, e.g., of neoplastic cells, or in animal models such as mice, rats, rabbits, dogs, or pigs. An animal model may also be used to determine the appropriate concentration range and route of administration. Such information can then be used to determine useful doses and routes for

5 administration in humans.

A therapeutically effective dose refers to that amount of active ingredient, for example MTRP or fragments thereof, antibodies of MTRP, and agonists, antagonists or inhibitors of MTRP, which ameliorates the symptoms or condition. Therapeutic efficacy and toxicity may be determined by standard pharmaceutical procedures in cell cultures or with experimental animals, such as by
10 calculating the ED_{50} (the dose therapeutically effective in 50% of the population) or LD_{50} (the dose lethal to 50% of the population) statistics. The dose ratio of toxic to therapeutic effects is the therapeutic index, which can be expressed as the LD_{50}/ED_{50} ratio. Pharmaceutical compositions which exhibit large therapeutic indices are preferred. The data obtained from cell culture assays and animal studies are used to formulate a range of dosage for human use. The dosage contained in such
15 compositions is preferably within a range of circulating concentrations that includes the ED_{50} with little or no toxicity. The dosage varies within this range depending upon the dosage form employed, the sensitivity of the patient, and the route of administration.

The exact dosage will be determined by the practitioner, in light of factors related to the subject requiring treatment. Dosage and administration are adjusted to provide sufficient levels of the
20 active moiety or to maintain the desired effect. Factors which may be taken into account include the severity of the disease state, the general health of the subject, the age, weight, and gender of the subject, time and frequency of administration, drug combination(s), reaction sensitivities, and response to therapy. Long-acting pharmaceutical compositions may be administered every 3 to 4 days, every week, or biweekly depending on the half-life and clearance rate of the particular
25 formulation.

Normal dosage amounts may vary from about 0.1 μg to 100,000 μg , up to a total dose of about 1 gram, depending upon the route of administration. Guidance as to particular dosages and methods of delivery is provided in the literature and generally available to practitioners in the art. Those skilled in the art will employ different formulations for nucleotides than for proteins or their
30 inhibitors. Similarly, delivery of polynucleotides or polypeptides will be specific to particular cells, conditions, locations, etc.

DIAGNOSTICS

In another embodiment, antibodies which specifically bind MTRP may be used for the diagnosis of disorders characterized by expression of MTRP, or in assays to monitor patients being

treated with MTRP or agonists, antagonists, or inhibitors of MTRP. Antibodies useful for diagnostic purposes may be prepared in the same manner as described above for therapeutics. Diagnostic assays for MTRP include methods which utilize the antibody and a label to detect MTRP in human body fluids or in extracts of cells or tissues. The antibodies may be used with or without modification, and
5 may be labeled by covalent or non-covalent attachment of a reporter molecule. A wide variety of reporter molecules, several of which are described above, are known in the art and may be used.

A variety of protocols for measuring MTRP, including ELISAs, RIAs, and FACS, are known in the art and provide a basis for diagnosing altered or abnormal levels of MTRP expression. Normal or standard values for MTRP expression are established by combining body fluids or cell extracts
10 taken from normal mammalian subjects, for example, human subjects, with antibody to MTRP under conditions suitable for complex formation. The amount of standard complex formation may be quantitated by various methods, such as photometric means. Quantities of MTRP expressed in subject, control, and disease samples from biopsied tissues are compared with the standard values. Deviation between standard and subject values establishes the parameters for diagnosing disease.

15 In another embodiment of the invention, the polynucleotides encoding MTRP may be used for diagnostic purposes. The polynucleotides which may be used include oligonucleotide sequences, complementary RNA and DNA molecules, and PNAs. The polynucleotides may be used to detect and quantify gene expression in biopsied tissues in which expression of MTRP may be correlated with disease. The diagnostic assay may be used to determine absence, presence, and excess
20 expression of MTRP, and to monitor regulation of MTRP levels during therapeutic intervention.

In one aspect, hybridization with PCR probes which are capable of detecting polynucleotide sequences, including genomic sequences, encoding MTRP or closely related molecules may be used to identify nucleic acid sequences which encode MTRP. The specificity of the probe, whether it is made from a highly specific region, e.g., the 5' regulatory region, or from a less specific region, e.g., a
25 conserved motif, and the stringency of the hybridization or amplification will determine whether the probe identifies only naturally occurring sequences encoding MTRP, allelic variants, or related sequences.

Probes may also be used for the detection of related sequences, and may have at least 50% sequence identity to any of the MTRP encoding sequences. The hybridization probes of the subject
30 invention may be DNA or RNA and may be derived from the sequence of SEQ ID NO:18-34 or from genomic sequences including promoters, enhancers, and introns of the MTRP gene.

Means for producing specific hybridization probes for DNAs encoding MTRP include the cloning of polynucleotide sequences encoding MTRP or MTRP derivatives into vectors for the production of mRNA probes. Such vectors are known in the art, are commercially available, and may

be used to synthesize RNA probes in vitro by means of the addition of the appropriate RNA polymerases and the appropriate labeled nucleotides. Hybridization probes may be labeled by a variety of reporter groups, for example, by radionuclides such as ^{32}P or ^{35}S , or by enzymatic labels, such as alkaline phosphatase coupled to the probe via avidin/biotin coupling systems, and the like.

- 5 Polynucleotide sequences encoding MTRP may be used for the diagnosis of disorders associated with expression of MTRP. Examples of such disorders include, but are not limited to, a membrane transport disorder such as cystinuria, dibasicaminoaciduria, hypercystinuria, lysinuria, hartnup disease, tryptophan malabsorption, methionine malabsorption, histidinuria, iminoglycinuria, dicarboxylicaminoaciduria, cystinosis, renal glycosuria, glucose-galactose malabsorption, familial
- 10 hypercholesterolemia, hypouricemia, familial hypophosphatemic rickets, congenital chloridorrhea, cystic fibrosis, familial goiter, distal renal tubular acidosis, Menkes' disease, lethal diarrhea, nephrogenic diabetes insipidus, juvenile pernicious anemia, folate malabsorption, adrenoleukodystrophy, hereditary myoglobinuria, Zellweger syndrome, hyperinsulinemic hypoglycemia, akinesia, amyotrophic lateral sclerosis, ataxia telangiectasia, cystic fibrosis, Becker's
- 15 muscular dystrophy, Bell's palsy, Charcot-Marie Tooth disease, diabetes mellitus, diabetes insipidus, diabetic neuropathy, Duchenne muscular dystrophy, hyperkalemic periodic paralysis, normokalemic periodic paralysis, Parkinson's disease, malignant hyperthermia, multidrug resistance, myasthenia gravis, myotonic dystrophy, catatonia, tardive dyskinesia, dystonias, peripheral neuropathy, cerebral neoplasms, and prostate cancer; a cardiac disorder associated with transport such as angina,
- 20 bradyarrhythmia, tachyarrhythmia, hypertension, Long QT syndrome, myocarditis, cardiomyopathy, nemaline myopathy, centronuclear myopathy, lipid myopathy, mitochondrial myopathy, thyrotoxic myopathy, ethanol myopathy, dermatomyositis, inclusion body myositis, infectious myositis, and polymyositis; a neurological disorder associated with transport such as Alzheimer's disease, amnesia, bipolar disorder, dementia, depression, epilepsy, Tourette's disorder, paranoid psychoses, and
- 25 schizophrenia; and an other disorder associated with transport such as neurofibromatosis, postherpetic neuralgia, trigeminal neuropathy, sarcoidosis, sickle cell anemia, Wilson's disease, cataracts, infertility, pulmonary artery stenosis, sensorineural autosomal deafness, hyperglycemia, hypoglycemia, Grave's disease, goiter, Cushing's disease, Addison's disease, glucose-galactose malabsorption syndrome, and hypercholesterolemia; an immune/inflammatory disorder such as
- 30 acquired immunodeficiency syndrome (AIDS), Addison's disease, adult respiratory distress syndrome, allergies, ankylosing spondylitis, amyloidosis, anemia, asthma, atherosclerosis, autoimmune hemolytic anemia, autoimmune thyroiditis, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), bronchitis, cholecystitis, contact dermatitis, Crohn's disease, atopic dermatitis, dermatomyositis, diabetes mellitus, emphysema, episodic lymphopenia

with lymphocytotoxins; erythroblastosis fetalis, erythema nodosum, atrophic gastritis, glomerulonephritis, Goodpasture's syndrome, gout, Graves' disease, Hashimoto's thyroiditis, hypereosinophilia, irritable bowel syndrome, multiple sclerosis, myasthenia gravis, myocardial or pericardial inflammation, osteoarthritis, osteoporosis, pancreatitis, polymyositis, psoriasis, Reiter's syndrome, rheumatoid arthritis, scleroderma, Sjögren's syndrome, systemic anaphylaxis, systemic lupus erythematosus, systemic sclerosis, thrombocytopenic purpura, ulcerative colitis, uveitis, Werner syndrome, complications of cancer, hemodialysis, and extracorporeal circulation; a viral, bacterial, fungal, parasitic, protozoal, or helminthic infection; and trauma; a cell proliferative disorder such as actinic keratosis, arteriosclerosis, atherosclerosis, bursitis, cirrhosis, hepatitis, mixed connective tissue disease (MCTD), myelofibrosis, paroxysmal nocturnal hemoglobinuria, polycythemia vera, psoriasis, primary thrombocythemia; and a cancer including adenocarcinoma, leukemia, lymphoma, melanoma, myeloma, sarcoma, teratocarcinoma; and, in particular, a cancer of the adrenal gland, bladder, bone, bone marrow, brain, breast, cervix, gall bladder, ganglia, gastrointestinal tract, heart, kidney, liver, lung, muscle, ovary, pancreas, parathyroid, penis, prostate, salivary glands, skin, spleen, testis, thymus, thyroid, and uterus. The polynucleotide sequences encoding MTRP may be used in Southern or northern analysis, dot blot, or other membrane-based technologies; in PCR technologies; in dipstick, pin, and multiformat ELISA-like assays; and in microarrays utilizing fluids or tissues from patients to detect altered MTRP expression. Such qualitative or quantitative methods are well known in the art.

In a particular aspect, the nucleotide sequences encoding MTRP may be useful in assays that detect the presence of associated disorders, particularly those mentioned above. The nucleotide sequences encoding MTRP may be labeled by standard methods and added to a fluid or tissue sample from a patient under conditions suitable for the formation of hybridization complexes. After a suitable incubation period, the sample is washed and the signal is quantified and compared with a standard value. If the amount of signal in the patient sample is significantly altered in comparison to a control sample then the presence of altered levels of nucleotide sequences encoding MTRP in the sample indicates the presence of the associated disorder. Such assays may also be used to evaluate the efficacy of a particular therapeutic treatment regimen in animal studies, in clinical trials, or to monitor the treatment of an individual patient.

In order to provide a basis for the diagnosis of a disorder associated with expression of MTRP, a normal or standard profile for expression is established. This may be accomplished by combining body fluids or cell extracts taken from normal subjects, either animal or human, with a sequence, or a fragment thereof, encoding MTRP, under conditions suitable for hybridization or amplification. Standard hybridization may be quantified by comparing the values obtained from

normal subjects with values from an experiment in which a known amount of a substantially purified polynucleotide is used. Standard values obtained in this manner may be compared with values obtained from samples from patients who are symptomatic for a disorder. Deviation from standard values is used to establish the presence of a disorder.

5 Once the presence of a disorder is established and a treatment protocol is initiated, hybridization assays may be repeated on a regular basis to determine if the level of expression in the patient begins to approximate that which is observed in the normal subject. The results obtained from successive assays may be used to show the efficacy of treatment over a period ranging from several days to months.

10 With respect to cancer, the presence of an abnormal amount of transcript (either under- or overexpressed) in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development
15 or further progression of the cancer.

Additional diagnostic uses for oligonucleotides designed from the sequences encoding MTRP may involve the use of PCR. These oligomers may be chemically synthesized, generated enzymatically, or produced in vitro. Oligomers will preferably contain a fragment of a polynucleotide encoding MTRP, or a fragment of a polynucleotide complementary to the polynucleotide encoding
20 MTRP, and will be employed under optimized conditions for identification of a specific gene or condition. Oligomers may also be employed under less stringent conditions for detection or quantification of closely related DNA or RNA sequences.

Methods which may also be used to quantify the expression of MTRP include radiolabeling or biotinylating nucleotides, coamplification of a control nucleic acid, and interpolating results from
25 standard curves. (See, e.g., Melby, P.C. et al. (1993) J. Immunol. Methods 159:235-244; Duplaa, C. et al. (1993) Anal. Biochem. 212:229-236.) The speed of quantitation of multiple samples may be accelerated by running the assay in a high-throughput format where the oligomer of interest is presented in various dilutions and a spectrophotometric or colorimetric response gives rapid quantitation.

30 In further embodiments, oligonucleotides or longer fragments derived from any of the polynucleotide sequences described herein may be used as targets in a microarray. The microarray can be used to monitor the expression level of large numbers of genes simultaneously and to identify genetic variants, mutations, and polymorphisms. This information may be used to determine gene function, to understand the genetic basis of a disorder, to diagnose a disorder, and to develop and

monitor the activities of therapeutic agents.

Microarrays may be prepared, used, and analyzed using methods known in the art. (See, e.g., Brennan, T.M. et al. (1995) U.S. Patent No. 5,474,796; Schena, M. et al. (1996) Proc. Natl. Acad. Sci. USA 93:10614-10619; Baldeschweiler et al. (1995) PCT application WO95/251116; Shalon, D. et al. 5 (1995) PCT application WO95/35505; Heller, R.A. et al. (1997) Proc. Natl. Acad. Sci. USA 94:2150-2155; and Heller, M.J. et al. (1997) U.S. Patent No. 5,605,662.)

In another embodiment of the invention, nucleic acid sequences encoding MTRP may be used to generate hybridization probes useful in mapping the naturally occurring genomic sequence. The sequences may be mapped to a particular chromosome, to a specific region of a chromosome, or to 10 artificial chromosome constructions, e.g., human artificial chromosomes (HACs), yeast artificial chromosomes (YACs), bacterial artificial chromosomes (BACs), bacterial P1 constructions, or single chromosome cDNA libraries. (See, e.g., Harrington, J.J. et al. (1997) Nat. Genet. 15:345-355; Price, C.M. (1993) Blood Rev. 7:127-134; and Trask, B.J. (1991) Trends Genet. 7:149-154.)

Fluorescent in situ hybridization (FISH) may be correlated with other physical chromosome 15 mapping techniques and genetic map data. (See, e.g., Heinz-Ulrich, et al. (1995) in Meyers, supra, pp. 965-968.) Examples of genetic map data can be found in various scientific journals or at the Online Mendelian Inheritance in Man (OMIM) World Wide Web site. Correlation between the location of the gene encoding MTRP on a physical chromosomal map and a specific disorder, or a predisposition to a specific disorder, may help define the region of DNA associated with that disorder. 20 The nucleotide sequences of the invention may be used to detect differences in gene sequences among normal, carrier, and affected individuals.

In situ hybridization of chromosomal preparations and physical mapping techniques, such as linkage analysis using established chromosomal markers, may be used for extending genetic maps. Often the placement of a gene on the chromosome of another mammalian species, such as mouse, 25 may reveal associated markers even if the number or arm of a particular human chromosome is not known. New sequences can be assigned to chromosomal arms by physical mapping. This provides valuable information to investigators searching for disease genes using positional cloning or other gene discovery techniques. Once the disease or syndrome has been crudely localized by genetic linkage to a particular genomic region, e.g., ataxia-telangiectasia to 11q22-23, any sequences mapping 30 to that area may represent associated or regulatory genes for further investigation. (See, e.g., Gatti, R.A. et al. (1988) Nature 336:577-580.) The nucleotide sequence of the subject invention may also be used to detect differences in the chromosomal location due to translocation, inversion, etc., among normal, carrier, or affected individuals.

In another embodiment of the invention, MTRP, its catalytic or immunogenic fragments, or

oligopeptides thereof can be used for screening libraries of compounds in any of a variety of drug screening techniques. The fragment employed in such screening may be free in solution, affixed to a solid support, borne on a cell surface, or located intracellularly. The formation of binding complexes between MTRP and the agent being tested may be measured.

5 Another technique for drug screening provides for high throughput screening of compounds having suitable binding affinity to the protein of interest. (See, e.g., Geysen, et al. (1984) PCT application WO84/03564.) In this method, large numbers of different small test compounds are synthesized on a solid substrate. The test compounds are reacted with MTRP, or fragments thereof, and washed. Bound MTRP is then detected by methods well known in the art. Purified MTRP can
10 also be coated directly onto plates for use in the aforementioned drug screening techniques. Alternatively, non-neutralizing antibodies can be used to capture the peptide and immobilize it on a solid support.

In another embodiment, one may use competitive drug screening assays in which neutralizing antibodies capable of binding MTRP specifically compete with a test compound for binding MTRP.
15 In this manner, antibodies can be used to detect the presence of any peptide which shares one or more antigenic determinants with MTRP.

In additional embodiments, the nucleotide sequences which encode MTRP may be used in any molecular biology techniques that have yet to be developed, provided the new techniques rely on properties of nucleotide sequences that are currently known, including, but not limited to, such
20 properties as the triplet genetic code and specific base pair interactions.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific
25 embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

The disclosures of all patents, applications, and publications mentioned above and below, in particular U.S. Ser. No. [Attorney Docket No. PF-0633 P, filed November 4, 1998], U.S. Ser. No. [Attorney Docket No. PF-0645 P, filed November 24, 1998], U.S. Ser. No. [Attorney Docket No. PF-0657 P, filed December 22, 1998], and U.S. Ser. No. 60/121,896, are hereby expressly incorporated
30 by reference.

EXAMPLES

I. Construction of cDNA Libraries

RNA was purchased from Clontech or isolated from tissues described in Table 4. Some

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tissues were homogenized and lysed in guanidinium isothiocyanate, while others were homogenized and lysed in phenol or in a suitable mixture of denaturants, such as TRIZOL (Life Technologies), a monophasic solution of phenol and guanidine isothiocyanate. The resulting lysates were centrifuged over CsCl cushions or extracted with chloroform. RNA was precipitated from the lysates with either isopropanol or sodium acetate and ethanol, or by other routine methods.

Phenol extraction and precipitation of RNA were repeated as necessary to increase RNA purity. In some cases, RNA was treated with DNase. For most libraries, poly(A+) RNA was isolated using oligo d(T)-coupled paramagnetic particles (Promega), OLIGOTEX latex particles (QIAGEN, Chatsworth CA), or an OLIGOTEX mRNA purification kit (QIAGEN). Alternatively, RNA was isolated directly from tissue lysates using other RNA isolation kits, e.g., the POLY(A)PURE mRNA purification kit (Ambion, Austin TX).

In some cases, Stratagene was provided with RNA and constructed the corresponding cDNA libraries. Otherwise, cDNA was synthesized and cDNA libraries were constructed with the UNIZAP vector system (Stratagene) or SUPERScript plasmid system (Life Technologies), using the recommended procedures or similar methods known in the art. (See, e.g., Ausubel, 1997, supra, units 5.1-6.6.) Reverse transcription was initiated using oligo d(T) or random primers. Synthetic oligonucleotide adapters were ligated to double stranded cDNA, and the cDNA was digested with the appropriate restriction enzyme or enzymes. For most libraries, the cDNA was size-selected (300-1000 bp) using SEPHACRYL S1000, SEPHAROSE CL2B, or SEPHAROSE CL4B column chromatography (Amersham Pharmacia Biotech) or preparative agarose gel electrophoresis. cDNAs were ligated into compatible restriction enzyme sites of the polylinker of a suitable plasmid, e.g., PBLUESCRIPT plasmid (Stratagene), PSPORT1 plasmid (Life Technologies), or pINCY (Incyte Pharmaceuticals, Palo Alto CA). Recombinant plasmids were transformed into competent *E. coli* cells including XL1-Blue, XL1-BlueMRF, or SOLR from Stratagene or DH5 α , DH10B, or ElectroMAX DH10B from Life Technologies.

II. Isolation of cDNA Clones

Plasmids were recovered from host cells by in vivo excision using the UNIZAP vector system (Stratagene) or by cell lysis. Plasmids were purified using at least one of the following: a Magic or WIZARD Minipreps DNA purification system (Promega); an AGTC Miniprep purification kit (Edge Biosystems, Gaithersburg MD); and QIAWELL 8 Plasmid, QIAWELL 8 Plus Plasmid, QIAWELL 8 Ultra Plasmid purification systems or the R.E.A.L. PREP 96 plasmid purification kit from QIAGEN. Following precipitation, plasmids were resuspended in 0.1 ml of distilled water and stored, with or without lyophilization, at 4°C.

Alternatively, plasmid DNA was amplified from host cell lysates using direct link PCR in a

high-throughput format (Rao, V.B. (1994) Anal. Biochem. 216:1-14). Host cell lysis and thermal cycling steps were carried out in a single reaction mixture. Samples were processed and stored in 384-well plates, and the concentration of amplified plasmid DNA was quantified fluorometrically using PICOGREEN dye (Molecular Probes, Eugene OR) and a FLUOROSKAN II fluorescence scanner (Labsystems Oy, Helsinki, Finland).

III. Sequencing and Analysis

cDNA sequencing reactions were processed using standard methods or high-throughput instrumentation such as the ABI CATALYST 800 (Perkin-Elmer) thermal cycler or the PTC-200 thermal cycler (MJ Research) in conjunction with the HYDRA microdispenser (Robbins Scientific) or the MICROLAB 2200 (Hamilton) liquid transfer system. cDNA sequencing reactions were prepared using reagents provided by Amersham Pharmacia Biotech or supplied in ABI sequencing kits such as the ABI PRISM BIGDYE Terminator cycle sequencing ready reaction kit (Perkin-Elmer). Electrophoretic separation of cDNA sequencing reactions and detection of labeled polynucleotides were carried out using the MEGABACE 1000 DNA sequencing system (Molecular Dynamics); the ABI PRISM 373 or 377 sequencing system (Perkin-Elmer) in conjunction with standard ABI protocols and base calling software; or other sequence analysis systems known in the art. Reading frames within the cDNA sequences were identified using standard methods (reviewed in Ausubel, 1997, *supra*, unit 7.7). Some of the cDNA sequences were selected for extension using the techniques disclosed in Example V.

The polynucleotide sequences derived from cDNA sequencing were assembled and analyzed using a combination of software programs which utilize algorithms well known to those skilled in the art. Table 5 summarizes the tools, programs, and algorithms used and provides applicable descriptions, references, and threshold parameters. The first column of Table 5 shows the tools, programs, and algorithms used, the second column provides brief descriptions thereof, the third column presents appropriate references, all of which are incorporated by reference herein in their entirety, and the fourth column presents, where applicable, the scores, probability values, and other parameters used to evaluate the strength of a match between two sequences (the higher the score, the greater the homology between two sequences). Sequences were analyzed using MACDNASIS PRO software (Hitachi Software Engineering, South San Francisco CA) and LASERGENE software (DNASTAR). Polynucleotide and polypeptide sequence alignments were generated using the default parameters specified by the clustal algorithm as incorporated into the MEGALIGN multisequence alignment program (DNASTAR), which also calculates the percent identity between aligned sequences.

The polynucleotide sequences were validated by removing vector, linker, and polyA

sequences and by masking ambiguous bases, using algorithms and programs based on BLAST, dynamic programming, and dinucleotide nearest neighbor analysis. The sequences were then queried against a selection of public databases such as the GenBank primate, rodent, mammalian, vertebrate, and eukaryote databases, and BLOCKS, PRINTS, DOMO, PRODOM, and PFAM to acquire
5 annotation using programs based on BLAST, FASTA, and BLIMPS. The sequences were assembled into full length polynucleotide sequences using programs based on Phred, Phrap, and Consed, and were screened for open reading frames using programs based on GeneMark, BLAST, and FASTA. The full length polynucleotide sequences were translated to derive the corresponding full length amino acid sequences, and these full length sequences were subsequently analyzed by querying
10 against databases such as the GenBank databases (described above), SwissProt, BLOCKS, PRINTS, DOMO, PRODOM, Prosite, and Hidden Markov Model (HMM)-based protein family databases such as PFAM. HMM is a probabilistic approach which analyzes consensus primary structures of gene families. (See, e.g., Eddy, S.R. (1996) Curr. Opin. Struct. Biol. 6:361-365.)

The programs described above for the assembly and analysis of full length polynucleotide and
15 amino acid sequences were also used to identify polynucleotide sequence fragments from SEQ ID NO:18-34. Fragments from about 20 to about 4000 nucleotides which are useful in hybridization and amplification technologies were described in The Invention section above.

IV. Northern Analysis

Northern analysis is a laboratory technique used to detect the presence of a transcript of a
20 gene and involves the hybridization of a labeled nucleotide sequence to a membrane on which RNAs from a particular cell type or tissue have been bound. (See, e.g., Sambrook, supra, ch. 7; Ausubel, 1995, supra, ch. 4 and 16.)

Analogous computer techniques applying BLAST were used to search for identical or related molecules in nucleotide databases such as GenBank or LIFESEQ (Incyte Pharmaceuticals). This
25 analysis is much faster than multiple membrane-based hybridizations. In addition, the sensitivity of the computer search can be modified to determine whether any particular match is categorized as exact or similar. The basis of the search is the product score, which is defined as:

$$\frac{\% \text{ sequence identity} \times \% \text{ maximum BLAST score}}{100}$$

30 The product score takes into account both the degree of similarity between two sequences and the length of the sequence match. For example, with a product score of 40, the match will be exact within a 1% to 2% error, and, with a product score of 70, the match will be exact. Similar molecules are usually identified by selecting those which show product scores between 15 and 40, although lower scores may identify related molecules.

The results of northern analyses are reported as a percentage distribution of libraries in which the transcript encoding MTRP occurred. Analysis involved the categorization of cDNA libraries by organ/tissue and disease. The organ/tissue categories included cardiovascular, dermatologic, developmental, endocrine, gastrointestinal, hematopoietic/immune, musculoskeletal, nervous, reproductive, and urologic. The disease/condition categories included cancer, inflammation, trauma, cell proliferation, neurological, and pooled. For each category, the number of libraries expressing the sequence of interest was counted and divided by the total number of libraries across all categories. Percentage values of tissue-specific and disease- or condition-specific expression are reported in Table 3.

10 **V. Extension of MTRP Encoding Polynucleotides**

The full length nucleic acid sequences of SEQ ID NO:18-34 were produced by extension of an appropriate fragment of the full length molecule using oligonucleotide primers designed from this fragment. One primer was synthesized to initiate 5' extension of the known fragment, and the other primer, to initiate 3' extension of the known fragment. The initial primers were designed using
15 OLIGO 4.06 software (National Biosciences), or another appropriate program, to be about 22 to 30 nucleotides in length, to have a GC content of about 50% or more, and to anneal to the target sequence at temperatures of about 68°C to about 72°C. Any stretch of nucleotides which would result in hairpin structures and primer-primer dimerizations was avoided.

Selected human cDNA libraries were used to extend the sequence. If more than one
20 extension was necessary or desired, additional or nested sets of primers were designed.

High fidelity amplification was obtained by PCR using methods well known in the art. PCR was performed in 96-well plates using the PTC-200 thermal cycler (MJ Research, Inc.). The reaction mix contained DNA template, 200 nmol of each primer, reaction buffer containing Mg^{2+} , $(NH_4)_2SO_4$, and β -mercaptoethanol, Taq DNA polymerase (Amersham Pharmacia Biotech), ELONGASE enzyme
25 (Life Technologies), and Pfu DNA polymerase (Stratagene), with the following parameters for primer pair PCI A and PCI B: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 60°C, 1 min; Step 4: 68°C, 2 min; Step 5: Steps 2, 3, and 4 repeated 20 times; Step 6: 68°C, 5 min; Step 7: storage at 4°C. In the alternative, the parameters for primer pair T7 and SK+ were as follows: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 57°C, 1 min; Step 4: 68°C, 2 min; Step 5: Steps 2, 3, and 4 repeated 20 times;
30 Step 6: 68°C, 5 min; Step 7: storage at 4°C.

The concentration of DNA in each well was determined by dispensing 100 μ l PICOGREEN quantitation reagent (0.25% (v/v) PICOGREEN; Molecular Probes, Eugene OR) dissolved in 1X TE and 0.5 μ l of undiluted PCR product into each well of an opaque fluorimeter plate (Corning Costar, Acton MA), allowing the DNA to bind to the reagent. The plate was scanned in a Fluoroskan II

(Labsystems Oy, Helsinki, Finland) to measure the fluorescence of the sample and to quantify the concentration of DNA. A 5 μ l to 10 μ l aliquot of the reaction mixture was analyzed by electrophoresis on a 1 % agarose mini-gel to determine which reactions were successful in extending the sequence.

5 The extended nucleotides were desalted and concentrated, transferred to 384-well plates, digested with CviJI cholera virus endonuclease (Molecular Biology Research, Madison WI), and sonicated or sheared prior to religation into pUC 18 vector (Amersham Pharmacia Biotech). For shotgun sequencing, the digested nucleotides were separated on low concentration (0.6 to 0.8%) agarose gels, fragments were excised, and agar digested with Agar ACE (Promega). Extended clones
10 were religated using T4 ligase (New England Biolabs, Beverly MA) into pUC 18 vector (Amersham Pharmacia Biotech), treated with Pfu DNA polymerase (Stratagene) to fill-in restriction site overhangs, and transfected into competent *E. coli* cells. Transformed cells were selected on antibiotic-containing media, individual colonies were picked and cultured overnight at 37°C in 384-well plates in LB/2x carb liquid media.

15 The cells were lysed, and DNA was amplified by PCR using Taq DNA polymerase (Amersham Pharmacia Biotech) and Pfu DNA polymerase (Stratagene) with the following parameters: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 60°C, 1 min; Step 4: 72°C, 2 min; Step 5: steps 2, 3, and 4 repeated 29 times; Step 6: 72°C, 5 min; Step 7: storage at 4°C. DNA was quantified by PICOGREEN reagent (Molecular Probes) as described above. Samples with low DNA
20 recoveries were reamplified using the same conditions as described above. Samples were diluted with 20% dimethylsulfoxide (1:2, v/v), and sequenced using DYENAMIC energy transfer sequencing primers and the DYENAMIC DIRECT kit (Amersham Pharmacia Biotech) or the ABI PRISM BIGDYE Terminator cycle sequencing ready reaction kit (Perkin-Elmer).

 In like manner, the nucleotide sequences of SEQ ID NO:18-34 are used to obtain 5'
25 regulatory sequences using the procedure above, oligonucleotides designed for such extension, and an appropriate genomic library.

VI. Labeling and Use of Individual Hybridization Probes

 Hybridization probes derived from SEQ ID NO:18-34 are employed to screen cDNAs, genomic DNAs, or mRNAs. Although the labeling of oligonucleotides, consisting of about 20 base
30 pairs, is specifically described, essentially the same procedure is used with larger nucleotide fragments. Oligonucleotides are designed using state-of-the-art software such as OLIGO 4.06 software (National Biosciences) and labeled by combining 50 pmol of each oligomer, 250 μ Ci of [γ -³²P] adenosine triphosphate (Amersham Pharmacia Biotech), and T4 polynucleotide kinase (DuPont NEN, Boston MA). The labeled oligonucleotides are substantially purified using a

SEPHADEX G-25 superfine size exclusion dextran bead column (Amersham Pharmacia Biotech). An aliquot containing 10^7 counts per minute of the labeled probe is used in a typical membrane-based hybridization analysis of human genomic DNA digested with one of the following endonucleases: Ase I, Bgl II, Eco RI, Pst I, Xba I, or Pvu II (DuPont NEN).

5 The DNA from each digest is fractionated on a 0.7% agarose gel and transferred to nylon membranes (Nytran Plus, Schleicher & Schuell, Durham NH). Hybridization is carried out for 16 hours at 40°C. To remove nonspecific signals, blots are sequentially washed at room temperature under conditions of up to, for example, 0.1 x saline sodium citrate and 0.5% sodium dodecyl sulfate. Hybridization patterns are visualized using autoradiography or an alternative imaging means and
10 compared.

VII. Microarrays

A chemical coupling procedure and an ink jet device can be used to synthesize array elements on the surface of a substrate. (See, e.g., Baldeschweiler, supra.) An array analogous to a dot or slot blot may also be used to arrange and link elements to the surface of a substrate using thermal,
15 UV, chemical, or mechanical bonding procedures. A typical array may be produced by hand or using available methods and machines and contain any appropriate number of elements. After hybridization, nonhybridized probes are removed and a scanner used to determine the levels and patterns of fluorescence. The degree of complementarity and the relative abundance of each probe which hybridizes to an element on the microarray may be assessed through analysis of the scanned
20 images.

Full-length cDNAs, Expressed Sequence Tags (ESTs), or fragments thereof may comprise the elements of the microarray. Fragments suitable for hybridization can be selected using software well known in the art such as LASERGENE software (DNASTAR). Full-length cDNAs, ESTs, or fragments thereof corresponding to one of the nucleotide sequences of the present invention, or
25 selected at random from a cDNA library relevant to the present invention, are arranged on an appropriate substrate, e.g., a glass slide. The cDNA is fixed to the slide using, e.g., UV cross-linking followed by thermal and chemical treatments and subsequent drying. (See, e.g., Schena, M. et al. (1995) Science 270:467-470; Shalon, D. et al. (1996) Genome Res. 6:639-645.) Fluorescent probes are prepared and used for hybridization to the elements on the substrate. The substrate is analyzed by
30 procedures described above.

VIII. Complementary Polynucleotides

Sequences complementary to the MTRP-encoding sequences, or any parts thereof, are used to detect, decrease, or inhibit expression of naturally occurring MTRP. Although use of oligonucleotides comprising from about 15 to 30 base pairs is described, essentially the same

procedure is used with smaller or with larger sequence fragments. Appropriate oligonucleotides are designed using OLIGO 4.06 software (National Biosciences) and the coding sequence of MTRP. To inhibit transcription, a complementary oligonucleotide is designed from the most unique 5' sequence and used to prevent promoter binding to the coding sequence. To inhibit translation, a complementary oligonucleotide is designed to prevent ribosomal binding to the MTRP-encoding transcript.

IX. Expression of MTRP

Expression and purification of MTRP is achieved using bacterial or virus-based expression systems. For expression of MTRP in bacteria, cDNA is subcloned into an appropriate vector containing an antibiotic resistance gene and an inducible promoter that directs high levels of cDNA transcription. Examples of such promoters include, but are not limited to, the *trp-lac (tac)* hybrid promoter and the T5 or T7 bacteriophage promoter in conjunction with the *lac* operator regulatory element. Recombinant vectors are transformed into suitable bacterial hosts, e.g., BL21(DE3). Antibiotic resistant bacteria express MTRP upon induction with isopropyl beta-D-thiogalactopyranoside (IPTG). Expression of MTRP in eukaryotic cells is achieved by infecting insect or mammalian cell lines with recombinant Autographica californica nuclear polyhedrosis virus (AcMNPV), commonly known as baculovirus. The nonessential polyhedrin gene of baculovirus is replaced with cDNA encoding MTRP by either homologous recombination or bacterial-mediated transposition involving transfer plasmid intermediates. Viral infectivity is maintained and the strong polyhedrin promoter drives high levels of cDNA transcription. Recombinant baculovirus is used to infect Spodoptera frugiperda (Sf9) insect cells in most cases, or human hepatocytes, in some cases. Infection of the latter requires additional genetic modifications to baculovirus. (See Engelhard, E.K. et al. (1994) Proc. Natl. Acad. Sci. USA 91:3224-3227; Sandig, V. et al. (1996) Hum. Gene Ther. 7:1937-1945.)

In most expression systems, MTRP is synthesized as a fusion protein with, e.g., glutathione S-transferase (GST) or a peptide epitope tag, such as FLAG or 6-His, permitting rapid, single-step, affinity-based purification of recombinant fusion protein from crude cell lysates. GST, a 26-kilodalton enzyme from Schistosoma japonicum, enables the purification of fusion proteins on immobilized glutathione under conditions that maintain protein activity and antigenicity (Amersham Pharmacia Biotech). Following purification, the GST moiety can be proteolytically cleaved from MTRP at specifically engineered sites. FLAG, an 8-amino acid peptide, enables immunoaffinity purification using commercially available monoclonal and polyclonal anti-FLAG antibodies (Eastman Kodak). 6-His, a stretch of six consecutive histidine residues, enables purification on metal-chelate resins (QIAGEN). Methods for protein expression and purification are discussed in Ausubel (1995, supra, ch. 10 and 16). Purified MTRP obtained by these methods can be used directly in the

following activity assay.

X. Demonstration of MTRP Activity

ATPase activity associated with MTRP can be measured by hydrolysis of radiolabeled ATP- $[\gamma\text{-}^{32}\text{P}]$, separation of the hydrolysis products by chromatographic methods, and quantitation of the recovered ^{32}P using a scintillation counter. The reaction mixture contains ATP- $[\gamma\text{-}^{32}\text{P}]$ and varying amounts of MTRP in a suitable buffer incubated at 37°C for a suitable period of time. The reaction is terminated by acid precipitation with trichloroacetic acid and then neutralized with base, and an aliquot of the reaction mixture is subjected to membrane or filter paper-based chromatography to separate the reaction products. The amount of ^{32}P liberated is counted in a scintillation counter. The amount of radioactivity recovered is proportional to the ATPase activity of MTRP in the assay.

MTRP transport activity is assayed by measuring uptake of labeled substrates into *Xenopus laevis* oocytes. Oocytes at stages V and VI are injected with MTRP mRNA (10 ng per oocyte) and incubated for 3 days at 18°C in OR2 medium (82.5mM NaCl, 2.5 mM KCl, 1mM CaCl₂, 1mM MgCl₂, 1mM Na₂HPO₄, 5 mM Hepes, 3.8 mM NaOH, 50µg/ml gentamycin, pH 7.8) to allow expression of MTRP protein. Oocytes are then transferred to standard uptake medium (100mM NaCl, 2 mM KCl, 1mM CaCl₂, 1mM MgCl₂, 10 mM Hepes/Tris, pH 7.5). Uptake of various substrates (e.g., amino acids, sugars, drugs, and neurotransmitters) is initiated by adding a ^3H -labeled substrate to the oocytes. After 30 minutes of incubation, uptake is terminated by washing the oocytes three times in Na⁺-free medium. Incorporation of ^3H is measured, and compared with controls. MTRP transport activity is proportional to the level of internalized ^3H -labeled substrate.

XI. Functional Assays

MTRP function is assessed by expressing the sequences encoding MTRP at physiologically elevated levels in mammalian cell culture systems. cDNA is subcloned into a mammalian expression vector containing a strong promoter that drives high levels of cDNA expression. Vectors of choice include pCMV SPORT (Life Technologies) and pCR3.1 (Invitrogen, Carlsbad CA), both of which contain the cytomegalovirus promoter. 5-10 µg of recombinant vector are transiently transfected into a human cell line, for example, an endothelial or hematopoietic cell line, using either liposome formulations or electroporation. 1-2 µg of an additional plasmid containing sequences encoding a marker protein are co-transfected. Expression of a marker protein provides a means to distinguish transfected cells from nontransfected cells and is a reliable predictor of cDNA expression from the recombinant vector. Marker proteins of choice include, e.g., Green Fluorescent Protein (GFP; Clontech), CD64, or a CD64-GFP fusion protein. Flow cytometry (FCM), an automated, laser optics-based technique, is used to identify transfected cells expressing GFP or CD64-GFP and to evaluate the apoptotic state of the cells and other cellular properties. FCM detects and quantifies the uptake of

fluorescent molecules that diagnose events preceding or coincident with cell death. These events include changes in nuclear DNA content as measured by staining of DNA with propidium iodide; changes in cell size and granularity as measured by forward light scatter and 90 degree side light scatter; down-regulation of DNA synthesis as measured by decrease in bromodeoxyuridine uptake; alterations in expression of cell surface and intracellular proteins as measured by reactivity with specific antibodies; and alterations in plasma membrane composition as measured by the binding of fluorescein-conjugated Annexin V protein to the cell surface. Methods in flow cytometry are discussed in Ormerod, M.G. (1994) Flow Cytometry, Oxford, New York NY.

The influence of MTRP on gene expression can be assessed using highly purified populations of cells transfected with sequences encoding MTRP and either CD64 or CD64-GFP. CD64 and CD64-GFP are expressed on the surface of transfected cells and bind to conserved regions of human immunoglobulin G (IgG). Transfected cells are efficiently separated from nontransfected cells using magnetic beads coated with either human IgG or antibody against CD64 (DYNAL, Lake Success NY). mRNA can be purified from the cells using methods well known by those of skill in the art. Expression of mRNA encoding MTRP and other genes of interest can be analyzed by northern analysis or microarray techniques.

XII. Production of MTRP Specific Antibodies

MTRP substantially purified using polyacrylamide gel electrophoresis (PAGE; see, e.g., Harrington, M.G. (1990) *Methods Enzymol.* 182:488-495), or other purification techniques, is used to immunize rabbits and to produce antibodies using standard protocols.

Alternatively, the MTRP amino acid sequence is analyzed using LASERGENE software (DNASTAR) to determine regions of high immunogenicity, and a corresponding oligopeptide is synthesized and used to raise antibodies by means known to those of skill in the art. Methods for selection of appropriate epitopes, such as those near the C-terminus or in hydrophilic regions are well described in the art. (See, e.g., Ausubel, 1995, *supra*, ch. 11.)

Typically, oligopeptides of about 15 residues in length are synthesized using an ABI 431A peptide synthesizer (Perkin-Elmer) using fmoc-chemistry and coupled to KLH (Sigma-Aldrich, St. Louis MO) by reaction with N-maleimidobenzoyl-N-hydroxysuccinimide ester (MBS) to increase immunogenicity. (See, e.g., Ausubel, 1995, *supra*.) Rabbits are immunized with the oligopeptide-KLH complex in complete Freund's adjuvant. Resulting antisera are tested for antipeptide and anti-MTRP activity by, for example, binding the peptide or MTRP to a substrate, blocking with 1% BSA, reacting with rabbit antisera, washing, and reacting with radio-iodinated goat anti-rabbit IgG.

XIII. Purification of Naturally Occurring MTRP Using Specific Antibodies

Naturally occurring or recombinant MTRP is substantially purified by immunoaffinity

chromatography using antibodies specific for MTRP. An immunoaffinity column is constructed by covalently coupling anti-MTRP antibody to an activated chromatographic resin, such as CNBr-activated SEPHAROSE (Amersham Pharmacia Biotech). After the coupling, the resin is blocked and washed according to the manufacturer's instructions.

- 5 Media containing MTRP are passed over the immunoaffinity column, and the column is washed under conditions that allow the preferential absorbance of MTRP (e.g., high ionic strength buffers in the presence of detergent). The column is eluted under conditions that disrupt antibody/MTRP binding (e.g., a buffer of pH 2 to pH 3, or a high concentration of a chaotrope, such as urea or thiocyanate ion), and MTRP is collected.

10 **XIV. Identification of Molecules Which Interact with MTRP**

- MTRP, or biologically active fragments thereof, are labeled with ¹²⁵I Bolton-Hunter reagent. (See, e.g., Bolton A.E. and W.M. Hunter (1973) Biochem. J. 133:529-539.) Candidate molecules previously arrayed in the wells of a multi-well plate are incubated with the labeled MTRP, washed, and any wells with labeled MTRP complex are assayed. Data obtained using different concentrations of MTRP are used to calculate values for the number, affinity, and association of MTRP with the candidate molecules.
- 15

Various modifications and variations of the described methods and systems of the invention will be apparent to those skilled in the art without departing from the scope and spirit of the invention.

- 20 Although the invention has been described in connection with certain embodiments, it should be understood that the invention as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the described modes for carrying out the invention which are obvious to those skilled in molecular biology or related fields are intended to be within the scope of the following claims.

Table 1

| Protein SEQ ID NO: | Nucleotide SEQ ID NO: | Clone ID | Library | Fragments |
|-----------------------|--------------------------|-------------|-----------|---|
| 1 | 18 | 961344 | BRSTTUT03 | 642329R1 (BRSTNOT03), 961344H1 (BRSTTUT03), 3149970H1 (ADREN04), 3255621H1 (OVRTUT01), 4265773H1 (KIDNNOT32), 4641320H1 (FROSTMT03), 4875558H1 (COLDN0T01) |
| 2 | 19 | 3128782 | LUNGTUT12 | 148511X20R1 (FIBRNGT01), 580891H1 (BRAVXT05), 1304328F1 (PLACNOT02), 1469890T6 (PANCNTUT02), 1799816T6 (COLNNOT27), 1985910R6 (LUNGAST01), 2722244F6 (LUNGTUT10), 3128782F6 (LUNGTUT12), 3128782H1 (LUNGTUT12), 3276993F6 (PROSBPT06), SBWA03256F1 |
| 3 | 20 | 1720440 | BLADNOT06 | 744485R1 (BRAITUT01), 859118R1 (BRAITUT03), 944049T1 (ADREN0T03), 1432755R1 (BEPIN01), 1720440H1 (BLADNOT06), 1808737X11C1 (PROSTUT12), 1812106F6 (PROSTUT12), 2192988F6 (THYRTUT03), 2192988X13F1 (THYRTUT03), 2192988X14F1 (THYRTUT03), 3384757H1 (ESCGNCT04) |
| 4 | 21 | 2274290 | PROSNON01 | 1732422F6 (BRSTTUT08), 2098563H1 (BRAITUT02), 2274290H1 (PROSNON01), 2274290X326D2 (PROSNON01), 2598580F6 (UTRSNOT10), 2779864F6 (OVRTUT03), 2864759F6 (KIDNNOT20), 2864759T6 (KIDNNOT20), 3221871H1 (COLNNON03) |
| 5 | 22 | 2740029 | BRSTTUT14 | 966363H1 (BRSTNOT05), 1000112R1 (BRSTNOT03), 1647057F6 (PROSTUT09), 2740029H1 (BRSTTUT14), 2740029X309F1 (BRSTTUT14), 2740029X321F1 (BRSTTUT14), 5068692H1 (PANCNOT23), 5193978H1 (LUNLTUT04), SBOA03895D1 |
| 6 | 23 | 2414415 | HNT3AZT01 | 1508631H1 (LUNGN0T14), 1596418F1 (BRAIN0T14), 2414415F6 (HNT3AZT01), 2414415H1 (HNT3AZT01), 2414415X300D1 (HNT3AZT01), 2902794H1 (DRGCNOT01), 3080373H1 (BRAIUNT01), 3554689H1 (SYNONOT01), 3881949F6 (SPLNNOT11), 4996983H1 (MYEPTXT02) |
| 7 | 24 | 2466714 | THYRN0T08 | 627910R6 (KIDNNOT05), 2358261R6 (LUNGFET05), 2358464F6 (LUNGFET05), 2466714H1 (THYRN0T08), 2726053F6 (OVRTUT05), 3845383H1 (DENDNOT01), 4228854H1 (BRAMDIT01) |

Table 1 (cont.)

| Protein SEQ ID NO: | Nucleotide SEQ ID NO: | Clone ID | Library | Fragments |
|-----------------------|--------------------------|-------------|-----------|--|
| 8 | 25 | 2617942 | GBLANCT01 | 1311045F6 (COLNFET02), 1375061F6 (LUNGNOT10), 1580318F6 (DUODNOT01), 2016443F6 (ENDCN03), 2617942F6 (GBLANOT01), 2617942H1 (GBLANOT01), 2703625H1 (OVRTUT10) |
| 9 | 26 | 2945431 | BRAITUT23 | 782666T6 (MYOMNOT01), 2715384T6 (THYRN09), 2945431F6 (BRAITUT23), 2945431H1 (BRAITUT23), 4114919F6 (UTRSTUT07) |
| 10 | 27 | 4074113 | KIDNNOT26 | 1754278T6 (LIVRTUT01), 1830341T6 (THP1AZT01), 2122328T6 (BRSTNOT07), 4074113F6 (KIDNNOT26), 4074113H1 (KIDNNOT26) |
| 11 | 28 | 1413743 | BRAINOT12 | 1413743H1 (BRAINOT12), 2643096F6 (LUNGTUT08), SBWA04580V1, SBWA04306V1, SEWA00027V1, SBWA00447V1, SBWA00075V1, SBWA03280V1, SBWA00778V1 |
| 12 | 29 | 1733477 | BRSTTUT08 | 1733477H1 (BRSTTUT08), 1733477F6 (BRSTTUT08), 3346594F6 (BRAITUT24), 1696051F6 (COLNNOT23), SAFC01922F1, 3234341F6 (COLNUCT03), 2634476T6 (COLNTUT15), SBGA03249F1 |
| 13 | 30 | 2641908 | LUNGTUT08 | 2641908H1 (LUNGTUT08), SASA01215F1, SASB01010F1, SASB01616F1, SASA03523F1 |
| 14 | 31 | 2656554 | LUNGTUT09 | 2656554H1 (LUNGTUT09), 2656554F6 (LUNGTUT09), 2656554T6 (LUNGTUT09) |
| 15 | 32 | 2719228 | THYRN09 | 2719228H1 (THYRN09), 2719228F6 (THYRN09), 532553H1 (BRAINOT03), 1626110F6 (COLNPOT01), 1626488F6 (COLNPOT01), 2100947R6 (BRAITUT02), SBGA05174F1 |
| 16 | 33 | 3657824 | ENDPNOT02 | 3657824H1 (ENDPNCT02), 2450345F6 (ENDANOT01), 2756555H1 (THP1AZS08), SCBA01425V1, 2394519T6 (THP1AZT01) |
| 17 | 34 | 5378485 | BRAXNOT01 | 5378485H1 (BRAXNOT01), SCAA06347V1, 1570276F1 (UTRSTNOT05) |

Table 2

| SEQ ID NO: | Amino Acid Residues | Potential Phosphorylation Sites | Potential Glycosylation Sites | Signature Sequences | Identification/Homologies | Analytical Methods |
|------------|---------------------|---|-------------------------------|--|--|--|
| 1 | 384 | S375 S34 T33 T89 T102 S161 S246 T298 | | E1-E2 ATPase signatures: R85-D115, T106-I128 P-type cation transporter signature: I109-I128 Transmembrane domains: I330-W351, L271-I288 | E1-E2 ATPase [Mus musculus] (GI 2944187) | BLAST BLOCKS MOTIFS PFAM PRINTS |
| 2 | 846 | T80 S106 S22 T40 T109 S110 S141 S229 S245 S255 S288 T408 T614 T679 T707 S819 S24 S274 S293 T386 T450 T536 S568 T581 T610 T673 | N301 | ABC transporter signatures: F453-L467, G330-Q525, D652-Q816, L744-A758 ATP-binding (P-loop) domains: G337-T344, G659-S666 | ABC transporter protein isoform [Homo sapiens] (GI 2522534) | BLAST BLOCKS MOTIFS PFAM PRINTS ProfileScan SPScan |
| 3 | 511 | S183 S99 S385 T387 T39 T106 S240 T376 T461 Y111 Y151 Y194 Y353 | N195 N238 N258 N383 | AMP-binding enzyme motif: R4-V404 AMP-binding domain signature: K91-M144 Lipocalin signature: E2-M14 | Fatty acid transport protein [Homo sapiens] (GI 4206376) Fatty acid transport protein [Mus musculus] (GI 2612939) | BLAST MOTIFS PFAM PRINTS ProfileScan |

Table 2 (cont.)

| SEQ ID NO: | Amino Acid Residues | Potential Phosphorylation Sites | Potential Glycosylation Sites | Signature Sequences | Identification/ Homologies | Analytical Methods |
|------------|---------------------|---|-------------------------------|---|---|---|
| 4 | 718 | S303 T224 T390 S501 T547 S560 S579 S623 T675 S248 S274 T326 S629 T655 | N176 N229 N410 | ABC transporter domain: L595-L609 ABC transporter family signatures: G483-V499, L595-D626 ABC transporter transmembrane domain: L128-M408 ABC transporter nucleotide binding domain: G483-G668 ATP/GTP-binding site motif A: G490-T497 Transmembrane domain: F123-V144 | ABC transporter protein [Homo sapiens] (GI 4321407) SMDR1 [Schistosoma mansoni] (GI 425474) | BLAST BLOCKS MOTIFS PFAM HMM |
| 5 | 635 | S25 T55 S128 T172 S242 S284 T378 T140 S222 S283 T286 T549 | N138 N489 N498 N534 | Sodium:solute symporter family signature: M61-A467, N169-A216, T172-V217, G353-I383, I430-A467 Transmembrane domains: M27-Y45, F256-A276, I430-F448, V458-G480 | Sodium:solute symporter [Homo sapiens] (GI 4884550) | BLAST BLOCKS PFAM ProfileScan HMM |

Table 2 (cont.)

| SEQ ID NO: | Amino Acid Residues | Potential Phosphorylation Sites | Potential Glycosylation Sites | Signature Sequences | Identification/ Homologies | Analytical Methods |
|------------|---------------------|---|-------------------------------|--|---|--|
| 6 | 535 | T11 S61 S103 S179 S292 T305 S337 T363 S487 S502 Y109 | | Amino acid permeases signature: L36-K474 (from PFAM) Transmembrane domains: L76-L96, K111-Y131, S159-N176, I189-V207, N264-Y287, I422-F449, I451-W469 | SLC7A8 [Homo sapiens] (GI 4581470) Amino acid transporter (GI 3639058, SEQ ID NO:38) | BLAST BLOCKS MOTIFS PFAM |
| 7 | 456 | T106 S107 S215 S277 T306 T331 S419 S425 | | Aromatic amino acid permease signature: N53-S98 (from BLOCKS) Transmembrane domains: F47-V69, Y68-L88, T169-L191, L197-I216, S366-Y387, M330-I347, F432-I454 | Aromatic amino acid transporter (GI 1840045, SEQ ID NO:39) | BLAST BLOCKS MOTIFS |
| 8 | 325 | T23 T29 S65 T84 S106 S133 S160 | | Transmembrane domains: I209-D227, I284-T307 | UDP-N-acetylglucosamine transporter [Canis familiaris] (GI 3298605) | BLAST MOTIFS |
| 9 | 178 | S4 T22 S132 T151 | | ABC transporters signature: S2-G141 (from PFAM) | ABC transporter (GI 3335175, SEQ ID NO:41) | BLAST BLOCKS MOTIFS PFAM Profilescan |

Table 2 (cont.)

| SEQ ID NO: | Amino Acid Residues | Potential Phosphorylation Sites | Potential Glycosylation Sites | Signature Sequences | Identification/ Homologies | Analytical Methods |
|------------|---------------------|--|-------------------------------|---|---|--|
| 10 | 255 | T89 S107 S214 | | ABC transporters signature: Q45-G227 (from PFAM) | Anthracycline resistance-associated protein (ABC transporter; GI 1279457, SEQ ID NO:42) | BLAST BLOCKS MOTIFS PFAM Profilescan |
| 11 | 462 | T179 S11 S37 T114 S420 T174 | | Aromatic amino acid permease signatures: F58-A104, A243-F265, L375-K394 | Transmembrane transporter [Schizosaccharomyces pombe] (GI 3367790) | BLAST MOTIFS PRINTS |
| 12 | 758 | T174 T251 S376 T615 S616 S633 S678 S713 S733 T138 S574 S603 T656 S687 T726 Y703 | N167 N172 N614 | Sulfate transporter signature: L198-T508 | Transporter [Mus musculus] (GI 5359730) Transporter [Homo sapiens] (GI 291964) | BLAST MOTIFS PFAM |
| 13 | 336 | T32 S99 S254 T274 S103 T104 T133 S273 | N116 | Transmembrane domains: L211-G230, A175-L196, W42-F61, F139-F159 | Organic anion transporter OATP-B [Homo sapiens] (GI 5006263) | BLAST HMM MOTIFS |
| 14 | 103 | S9 S92 Y14 | N81 | Transmembrane domain: V22-F41 | Similar to Human Na ⁺ /H ⁺ exchanger 2 [A57644] [Homo sapiens] (GI 1665827) | BLAST HMM MOTIFS |

Table 2 (cont.)

| SEQ ID NO: | Amino Acid Residues | Potential Phosphorylation Sites | Potential Glycosylation Sites | Signature Sequences | Identification/ Homologies | Analytical Methods |
|------------|---------------------|---------------------------------|-------------------------------|------------------------|--|------------------------|
| 15 | 123 | S21 S118 T119 | N39 | Signal peptide: M1-S21 | Similar to Sugar transporter [Caenorhabditis elegans] (GI 3878537) | BLAST HMM MOTIFS |
| 16 | 222 | T83 S61 S74 | | | E. coli cation transport protein (GI495778) | BLAST MOTIFS |
| 17 | 111 | | N100 | | Vacuolar proton-ATPase subunit M9.2 [Homo sapiens] (GI 2584789) | BLAST MOTIFS |

Table 3

| Nucleotide SEQ ID NO: | Tissue Expression (Fraction of Total) | Disease or Condition (Fraction of Total) | Vector |
|--------------------------|---|--|---------|
| 18 | Reproductive (0.292) Nervous (0.167) Hematopoietic/Immune (0.125) | Cell proliferative (0.750) Inflammation (0.208) | PSPORT1 |
| 19 | Reproductive (0.264) Nervous (0.155) Hematopoietic/Immune (0.145) | Cell proliferative (0.691) Inflammation (0.236) | pINCY |
| 20 | Reproductive Nervous Gastrointestinal | Cell proliferation (0.66) Inflammation and immune response (0.24) | pINCY |
| 21 | Reproductive Nervous Gastrointestinal Hematopoietic/Immune | Cell proliferation (0.73) Inflammation and immune response (0.21) | PSPORT1 |
| 22 | Nervous Reproductive | Cell proliferation (0.76) Inflammation and immune response (0.33) | pINCY |
| 23 | Reproductive (0.333) Nervous (0.296) | Cancer (0.519) Inflammation (0.185) | |
| 24 | Reproductive (0.250) Musculoskeletal (0.179) Hematopoietic/Immune (0.143) | Cancer (0.429) Inflammation (0.286) | |
| 25 | Reproductive (0.360) Gastrointestinal (0.200) Cardiovascular (0.120) | Cancer (0.520) Inflammation (0.160) | |
| 26 | Nervous (0.267) Endocrine (0.133) | Cancer (0.533) Inflammation (0.333) | |

Table 3 (cont.)

| Nucleotide SEQ ID NO: | Tissue Expression (Fraction of Total) | Disease or Condition (Fraction of Total) | Vector |
|--------------------------|---|--|--------|
| 27 | Urologic (0.333) Cardiovascular (0.167) Developmental (0.167) | Cancer (0.667) Inflammation (0.167) | |
| 28 | Nervous (0.222) Hematopoietic/Immune (0.185) Reproductive (0.185) | Cell Proliferation (0.481) Inflammation (0.407) | pINCY |
| 29 | Gastrointestinal (0.286) Reproductive (0.257) Nervous (0.200) | Cell Proliferation (0.743) Inflammation (0.286) | pINCY |
| 30 | Cardiovascular (0.400) Nervous (0.200) Reproductive (0.200) Gastrointestinal (0.200) | Cell Proliferation (0.800) Inflammation (0.200) | pINCY |
| 31 | Hematopoietic/Immune (0.500) Reproductive (0.250) Cardiovascular (0.250) | Cell Proliferation (0.750) Inflammation (0.500) | pINCY |
| 32 | Gastrointestinal (0.304) Hematopoietic/Immune (0.174) Nervous (0.174) | Cell Proliferation (0.826) Inflammation (0.347) | pINCY |
| 33 | Cardiovascular (0.238) Nervous (0.190) Hematopoietic/Immune (0.143) | Cell Proliferation (0.571) Inflammation (0.473) | pINCY |
| 34 | Nervous (0.510) Cardiovascular (0.102) | Cell Proliferation (0.612) Inflammation (0.266) | pINCY |

PF-0633 PCT

Table 4

| Nucleotide SEQ ID NO: | Library | Library Comment |
|--------------------------|-----------|---|
| 18 | BRSTTUT03 | Library was constructed using RNA isolated from breast tumor tissue removed from a 58-year-old Caucasian female during a unilateral extended simple mastectomy. Pathology indicated multicentric invasive grade 4 lobular carcinoma. The mass was identified in the upper outer quadrant, and three separate nodules were found in the lower outer quadrant of the left breast. Patient history included skin cancer, rheumatic heart disease, osteoarthritis, and tuberculosis. Family history included cerebrovascular disease, coronary artery aneurysm, breast cancer, prostate cancer, atherosclerotic coronary artery disease, and type I diabetes. |
| 19 | LUNGTUT12 | Library was constructed using RNA isolated from tumorous lung tissue removed from a 70-year-old Caucasian female during a lung lobectomy of the left upper lobe. Pathology indicated grade 3 (of 4) adenocarcinoma and vascular invasion. Patient history included tobacco abuse, depressive disorder, anxiety state, and skin cancer. Family history included cerebrovascular disease, congestive heart failure, colon cancer, depressive disorder, and primary liver cancer. |
| 20 | BLADNOT06 | Library was constructed using RNA isolated from posterior wall bladder tissue removed from a 66-year-old Caucasian male during a radical prostatectomy, radical cystectomy, and urinary diversion. Pathology for the associated tumor tissue indicated grade 3 transitional cell carcinoma on the anterior wall of the bladder and urothelium. Patient history included lung neoplasm. Family history included a malignant breast neoplasm, tuberculosis, cerebrovascular disease, atherosclerotic coronary artery disease, and lung cancer. |
| 21 | PROSNON01 | Normalized prostate library was constructed from 4.4 million independent clones from a prostate library. Starting RNA was made from prostate tissue removed from a 28-year-old Caucasian male. The normalization and hybridization conditions were adapted from Soares, M.B. et al. (1994) Proc. Natl. Acad. Sci. USA 91:9228-9232, using a longer (19 hour) reannealing hybridization period. |

Table 4 (cont.)

| Nucleotide SEQ ID NO: | Library | Library Comment |
|--------------------------|-----------|---|
| 22 | BRSTTUT14 | Library was constructed using RNA isolated from breast tumor tissue removed from a 62-year-old Caucasian female during a unilateral extended simple mastectomy. Pathology indicated an invasive grade 3 (of 4), nuclear grade 3 (of 3) adenocarcinoma, ductal type. Ductal carcinoma in situ, comedo type, comprised 60% of the tumor mass. Metastatic adenocarcinoma was identified in one (of 14) axillary lymph nodes with no perinodal extension. Tumor cells were strongly positive for estrogen receptors and weakly positive for progesterone receptors. Patient history included benign colon neoplasm, hyperlipidemia, cardiac dysrhythmia, and obesity. Family history included atherosclerotic coronary artery disease, myocardial infarction, colon cancer, ovarian cancer, lung cancer, and cerebrovascular disease. |
| 23 | HNT3AZT01 | Library was constructed using RNA isolated from the hNT2 cell line (derived from a human teratocarcinoma that exhibited properties characteristic of a committed neuronal precursor). Cells were treated for three days with 0.35 micromolar 5-aza-2'-deoxycytidine (A2). |
| 24 | THYNOT08 | Library was constructed using RNA isolated from the diseased left thyroid tissue removed from a 13-year-old Caucasian female during a complete thyroidectomy. Pathology indicated lymphocytic thyroiditis. |
| 25 | GBLANOT01 | Library was constructed using RNA isolated from diseased gallbladder tissue removed from a 53-year-old Caucasian female during a cholecystectomy. Pathology indicated mild chronic cholecystitis and cholelithiasis with approximately 150 mixed gallstones. Family history included benign hypertension. |
| 26 | BRAITUT23 | Library was constructed using RNA isolated from left posterior brain tumor tissue removed from a 36-year-old male during a cerebral meninges lesion excision. Pathology indicated meningioma. Family history included malignant skin melanoma, atherosclerotic coronary artery disease, hyperlipidemia, Huntington's chorea, and rheumatoid arthritis. |

Table 4 (cont.)

| Nucleotide SEQ ID NO: | Library | Library Comment |
|--------------------------|-----------|---|
| 27 | KIDNNOT26 | Library was constructed using RNA isolated from left kidney medulla and cortex tissue removed from a 53-year-old Caucasian female during a nephroureterectomy. Patient history included hyperlipidemia, cardiac dysrhythmia, metrorrhagia, cerebrovascular disease, and atherosclerotic coronary artery disease. |
| 28 | BRAINOT12 | Library was constructed using RNA isolated from brain tissue removed from the right frontal lobe of a 5-year-old Caucasian male during a hemispherectomy. Pathology indicated extensive polymicrogyria and mild to moderate gliosis (predominantly subpial and subcortical), which are consistent with chronic seizure disorder. The patient presented with intractable convulsive epilepsy. Family history included a cervical neoplasm. |
| 29 | BRSTTUT08 | Library was constructed using RNA isolated from breast tumor tissue removed from a 45-year-old Caucasian female during unilateral extended simple mastectomy. Pathology indicated invasive nuclear grade 2-3 adenocarcinoma (ductal type), with 3 of 23 lymph nodes positive for metastatic disease. Greater than 50% of the tumor volume was in-situ, both comedo and non-comedo types. There were also positive estrogen/progesterone receptors and uninvolved tissue showing proliferative changes. Patient history included valvuloplasty of mitral valve without replacement, rheumatic mitral insufficiency, and rheumatic heart disease. Family history included acute myocardial infarction and atherosclerotic coronary artery disease and type II diabetes. |

Table 4 (cont.)

| Nucleotide SEQ ID NO: | Library | Library Comment |
|--------------------------|-----------|--|
| 30 | LUNGTUT08 | <p>Library was constructed using RNA isolated from lung tumor tissue removed from a 63-year-old Caucasian male during a right upper lobectomy with fiberoptic bronchoscopy. Pathology indicated a grade 3 adenocarcinoma, forming a mass penetrating the pleura of the right upper lung lobe. The bronchial margin of the resection was free of tumor. The tissue from the superior segment of the right lower lobe lung showed multiple (2) calcified granulomas. Multiple lymph nodes were negative for tumor. In addition, budding yeast forms resembling histoplasma identified in two lymph nodes stained with GMS (silver). Patient history included atherosclerotic coronary artery disease, an acute myocardial infarction, rectal cancer, an asymptomatic abdominal aortic aneurysm, tobacco abuse, and cardiac dysrhythmia. Family history included congestive heart failure, stomach cancer, lung cancer, type II diabetes, atherosclerotic coronary artery disease, and acute myocardial infarction.</p> |
| 31 | LUNGTUT09 | <p>Library was constructed RNA isolated from lung tumor tissue removed from a 68-year-old Caucasian male during segmental lung resection. Pathology indicated invasive grade 3 squamous cell carcinoma in the right upper lobe, forming an infiltrating mass involving the bronchus and the surrounding parenchyma. One (of 4) intrapulmonary peribronchial lymph nodes contained a metastatic tumor. An apical cap was identified. One (of 15) right paratracheal lower lymph nodes contained a metastatic tumor. Permanent superior mediastinal sections revealed metastatic squamous cell carcinoma in the lymph nodes. Patient history included of type II diabetes, thyroid disorder, depressive disorder, hyperlipidemia, esophageal ulcer, and tobacco use. Family history included brain cancer and atherosclerotic coronary artery disease.</p> |

Table 4 (cont.)

| Nucleotide SEQ ID NO: | Library | Library Comment |
|--------------------------|-----------|--|
| 32 | THYRNOT09 | Library was constructed using RNA isolated from diseased thyroid tissue removed from an 18-year-old Caucasian female during an unilateral thyroid lobectomy and regional lymph node excision. Pathology indicated adenomatous goiter. This was associated with a follicular adenoma of the thyroid. The right neck lymph nodes displayed reactive follicular hyperplasia. The patient presented with hypophosphatemia. Patient history included compression of the brain, headache, iron deficiency anemia, active rickets, epidermal nevus syndrome (treated with lasers), and osteitis deformans. Family history included thyroid cancer, type II diabetes, benign hypertension, and nodular lymphoma. |
| 33 | ENDPNOT02 | Library was constructed using RNA isolated from pulmonary artery endothelial cells removed from a 10-year-old Caucasian male. The cells were treated with TNF alpha and IL-1 beta 10ng/ml each for 20 hours. |
| 34 | BRAXNOT01 | Library was constructed using RNA isolated from cerebellar tissue removed from a 70-year-old male. Patient history included chronic obstructive airways disease and left ventricular failure. |

Table 5

| Program | Description | Reference | Parameter Threshold |
|-------------------|---|--|---|
| ABI FACTURA | A program that removes vector sequences and masks ambiguous bases in nucleic acid sequences. | Perkin-Elmer Applied Biosystems, Foster City, CA. | |
| ABI/PARACEL FDF | A Fast Data Finder useful in comparing and annotating amino acid or nucleic acid sequences. | Perkin-Elmer Applied Biosystems, Foster City, CA; Paracel Inc., Pasadena, CA. | Mismatch <50% |
| ABI AutoAssembler | A program that assembles nucleic acid sequences. | Perkin-Elmer Applied Biosystems, Foster City, CA. | |
| BLAST | A Basic Local Alignment Search Tool useful in sequence similarity search for amino acid and nucleic acid sequences. BLAST includes five functions: blastp, blastn, blastx, tblastn, and tblastx. | Altschul, S.F. et al. (1990) J. Mol. Biol. 215:403-410; Altschul, S.F. et al. (1997) Nucleic Acids Res. 25: 3389-3402. | ESTs: Probability value= 1.0E-8 or less Full Length sequences: Probability value= 1.0E-10 or less |
| FASTA | A Pearson and Lipman algorithm that searches for similarity between a query sequence and a group of sequences of the same type. FASTA comprises at least five functions: fasta, tfasta, fastx, tfastx, and ssearch. | Pearson, W.R. and D.J. Lipman (1988) Proc. Natl. Acad. Sci. 85:2444-2448; Pearson, W.R. (1990) Methods Enzymol. 183: 63-98; and Smith, T.F. and M. S. Waterman (1981) Adv. Appl. Math. 2:482-489. | ESTs: fasta E value=1.06E-6 Assembled ESTs: fasta Identity= 95% or greater and Match length=200 bases or greater, fastx E value=1.0E-8 or less Full Length sequences: fastx score=100 or greater |
| BLIMPS | A BLocks IMProved Searcher that matches a sequence against those in BLOCKS, PRINTS, DOMO, PRODOM, and PFAM databases to search for gene families, sequence homology, and structural fingerprint regions. | Henikoff, S. and J.G. Henikoff, Nucl. Acid Res., 19:6565-72, 1991. J.G. Henikoff and S. Henikoff (1996) Methods Enzymol. 266:88-105; and Attwood, T.K. et al. (1997) J. Chem. Inf. Comput. Sci. 37: 417-424. | Score=1000 or greater; Ratio of Score/Strength = 0.75 or larger, and, if applicable, Probability value= 1.0E-3 or less |
| HMMER | An algorithm for searching a query sequence against hidden Markov model (HMM)-based databases of protein family consensus sequences, such as PFAM. | Krogh, A. et al. (1994) J. Mol. Biol., 235:1501-1531; Sonnhammer, E.L.L. et al. (1988) Nucleic Acids Res. 26:320-322. | Score=10-50 bits for PFAM hits, depending on individual protein families |

Table 5 (cont.)

| Program | Description | Reference | Parameter Threshold |
|-------------|--|--|--|
| ProfileScan | An algorithm that searches for structural and sequence motifs in protein sequences that match sequence patterns defined in Prosite. | Gribskov, M. et al. (1988) CABIOS 4:61-66; Gribskov, et al. (1989) Methods Enzymol. 183:146-159; Bairoch, A. et al. (1997) Nucleic Acids Res. 25: 217-221. | Normalized quality score \geq GCG-specified "HIGH" value for that particular Prosite motif. Generally, score=1.4-2.1. |
| Phred | A base-calling algorithm that examines automated sequencer traces with high sensitivity and probability. | Ewing, B. et al. (1998) Genome Res. 8:175-185; Ewing, B. and P. Green (1998) Genome Res. 8:186-194. | |
| Phrap | A Philis Revised Assembly Program including SWAT and CrossMatch, programs based on efficient implementation of the Smith-Waterman algorithm, useful in searching sequence homology and assembling DNA sequences. | Smith, T.F. and M. S. Waterman (1981) Adv. Appl. Math. 2:482-489; Smith, T.F. and M. S. Waterman (1981) J. Mol. Biol. 147:195-197; and Green, P., University of Washington, Seattle, WA. | Score= 120 or greater; Match length= 56 or greater |
| Consed | A graphical tool for viewing and editing Phrap assemblies | Gordon, D. et al. (1998) Genome Res. 8:195-202. | |
| SPScan | A weight matrix analysis program that scans protein sequences for the presence of secretory signal peptides. | Nielson, H. et al. (1997) Protein Engineering 10:1-6; Claverie, J.M. and S. Audic (1997) CABIOS 12: 431-439. | Score=3.5 or greater |
| Motifs | A program that searches amino acid sequences for patterns that matched those defined in Prosite. | Bairoch et al. <u>supra</u> ; Wisconsin Package Program Manual, version 9, page M51-59, Genetics Computer Group, Madison, WI. | |

What is claimed is:

1. A substantially purified polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-17 and fragments thereof.
- 5 2. A substantially purified variant having at least 90% amino acid sequence identity to the amino acid sequence of claim 1.
3. An isolated and purified polynucleotide encoding the polypeptide of claim 1.
- 10 4. An isolated and purified polynucleotide variant having at least 90% polynucleotide sequence identity to the polynucleotide of claim 3.
5. An isolated and purified polynucleotide which hybridizes under stringent conditions
15 to the polynucleotide of claim 3.
6. An isolated and purified polynucleotide having a sequence which is complementary to the polynucleotide of claim 3.
- 20 7. A method for detecting a polynucleotide, the method comprising the steps of:
 - (a) hybridizing the polynucleotide of claim 6 to at least one nucleic acid in a sample, thereby forming a hybridization complex; and
 - (b) detecting the hybridization complex, wherein the presence of the hybridization complex correlates with the presence of the polynucleotide in the sample.
- 25 8. The method of claim 7 further comprising amplifying the polynucleotide prior to hybridization.
9. An isolated and purified polynucleotide comprising a polynucleotide sequence
30 selected from the group consisting of SEQ ID NO:18-34 and fragments thereof.
10. An isolated and purified polynucleotide variant having at least 90% polynucleotide sequence identity to the polynucleotide of claim 9.

11. An isolated and purified polynucleotide having a sequence which is complementary to the polynucleotide of claim 9.

12. An expression vector comprising at least a fragment of the polynucleotide of claim 3.

13. A host cell comprising the expression vector of claim 12.

14. A method for producing a polypeptide, the method comprising the steps of:

- a) culturing the host cell of claim 13 under conditions suitable for the expression of the polypeptide; and
- b) recovering the polypeptide from the host cell culture.

15. A pharmaceutical composition comprising the polypeptide of claim 1 in conjunction with a suitable pharmaceutical carrier.

16. A purified antibody which specifically binds to the polypeptide of claim 1.

17. A purified agonist of the polypeptide of claim 1.

18. A purified antagonist of the polypeptide of claim 1.

19. A method for treating or preventing a disorder associated with decreased expression or activity of MTRP, the method comprising administering to a subject in need of such treatment an effective amount of the pharmaceutical composition of claim 15.

20. A method for treating or preventing a disorder associated with increased expression or activity of MTRP, the method comprising administering to a subject in need of such treatment an effective amount of the antagonist of claim 18.

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FIGURE 1A

| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|-----|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|------------|------------|
| 47 | F | G | S | E | M | A | S | A | I | C | E | V | H | A | S | L | D | P | S | L | S | L | F | C | S | G | S | W | E | P | 1720440 |
| 181 | Y | G | G | E | M | A | A | V | A | E | V | S | E | Q | L | G | K | S | L | L | K | F | C | S | G | D | L | G | P | GI 2612939 | |
| 77 | G | A | V | P | P | S | T | E | H | L | D | P | L | L | K | D | A | P | K | - | H | L | P | S | C | P | D | K | G | F | 1720440 |
| 211 | E | S | I | L | P | D | T | Q | L | L | D | P | M | L | A | E | A | P | T | T | P | L | A | Q | A | P | G | K | G | M | GI 2612939 |
| 106 | T | D | K | L | F | Y | I | Y | T | S | G | T | T | G | L | P | K | A | A | I | V | V | H | S | R | Y | Y | R | M | A | 1720440 |
| 241 | D | D | R | L | F | Y | I | Y | T | S | G | T | T | G | L | P | K | A | A | I | V | V | H | S | R | Y | Y | R | I | A | GI 2612939 |
| 136 | A | L | V | Y | Y | G | F | R | M | R | P | N | D | I | V | Y | D | C | L | P | L | Y | H | S | A | G | N | I | V | G | 1720440 |
| 271 | A | F | G | H | S | Y | S | M | R | A | A | D | V | L | Y | D | C | L | P | L | Y | H | S | A | G | N | I | M | G | GI 2612939 | |
| 166 | I | G | Q | C | L | L | H | G | M | T | V | V | I | R | K | K | F | S | A | S | R | F | W | D | D | C | I | K | Y | N | 1720440 |
| 301 | V | G | Q | C | V | I | Y | G | L | T | V | V | L | R | K | K | F | S | A | S | R | F | W | D | D | C | V | K | Y | N | GI 2612939 |
| 196 | C | T | I | V | Q | Y | I | G | E | L | C | R | Y | L | L | N | Q | P | P | R | E | A | E | N | Q | H | Q | V | R | M | 1720440 |
| 331 | C | T | V | V | Q | Y | I | G | E | I | C | R | Y | L | L | R | Q | P | V | R | D | V | E | Q | R | H | R | V | R | L | GI 2612939 |

FIGURE 1B

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| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|-----|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|------------|
| 226 | A | L | G | N | G | L | R | Q | S | I | W | T | N | F | S | S | R | F | H | I | P | Q | V | A | E | F | Y | G | A | T | 1720440 |
| 361 | A | V | G | N | G | L | R | P | A | I | W | E | E | F | T | Q | R | F | G | V | P | Q | I | G | E | F | Y | G | A | T | GI 2612939 |
| 256 | E | C | N | C | S | L | G | N | F | D | S | Q | V | G | A | C | G | F | N | S | R | I | L | S | S | V | Y | P | I | R | 1720440 |
| 391 | E | C | N | C | S | I | A | N | M | D | G | K | V | G | S | C | G | F | N | S | R | I | L | T | H | V | Y | P | I | R | GI 2612939 |
| 286 | L | V | R | V | N | E | D | T | M | E | L | I | R | G | P | D | G | V | C | I | P | C | Q | P | G | E | P | G | Q | L | 1720440 |
| 421 | L | V | K | V | N | E | D | T | M | E | P | L | R | D | S | E | G | L | C | I | P | C | Q | P | G | E | P | G | L | L | GI 2612939 |
| 316 | V | G | R | I | I | Q | K | D | P | L | R | R | F | D | G | Y | L | N | Q | G | A | N | N | K | K | I | A | K | D | V | 1720440 |
| 451 | V | G | Q | I | N | Q | Q | D | P | L | R | R | F | D | G | Y | V | S | D | S | A | T | N | K | K | I | A | H | S | V | GI 2612939 |
| 346 | F | K | K | G | D | Q | A | Y | L | T | G | D | V | L | V | M | D | E | L | G | Y | L | Y | F | R | D | R | T | G | D | 1720440 |
| 481 | F | R | K | G | D | S | A | Y | L | S | G | D | V | L | V | M | D | E | L | G | Y | M | Y | F | R | D | R | S | G | D | GI 2612939 |
| 376 | T | F | R | W | K | G | E | N | V | S | T | T | E | V | E | G | T | L | S | R | L | L | D | M | A | D | V | A | V | Y | 1720440 |
| 511 | T | F | R | W | R | G | E | N | V | S | T | T | E | V | E | A | V | L | S | R | L | L | G | Q | T | D | V | A | V | Y | GI 2612939 |

FIGURE 1C

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| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|-----|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|------------|---|---|---|---|---|---|---|---|---|---|---|---|---|------------|
| 406 | G | V | E | V | P | G | T | E | G | R | A | G | M | A | A | V | A | S | P | T | G | N | C | D | L | E | R | F | A | Q | 1720440 |
| 541 | G | V | A | V | P | G | V | E | G | K | A | G | M | A | A | I | A | D | P | H | S | Q | L | D | P | N | S | M | Y | Q | GI 2612939 |
| 436 | V | L | E | K | E | L | P | L | Y | A | R | P | I | F | L | R | L | L | P | E | L | H | K | T | G | T | Y | K | F | Q | 1720440 |
| 571 | E | L | Q | K | V | L | A | S | Y | A | R | P | I | F | L | R | L | L | P | Q | V | D | T | T | G | T | F | K | I | Q | GI 2612939 |
| 466 | K | T | E | L | R | K | E | G | F | D | P | A | I | V | K | D | P | L | F | Y | L | D | A | Q | K | G | R | Y | V | P | 1720440 |
| 601 | K | T | R | L | Q | R | E | G | F | D | P | R | Q | T | S | D | R | L | F | F | L | D | L | K | Q | G | R | Y | V | P | GI 2612939 |
| 496 | L | D | Q | E | A | Y | S | R | I | Q | A | G | E | E | K | L | 1720440 | | | | | | | | | | | | | | |
| 631 | L | D | E | R | V | H | A | R | I | C | A | G | D | F | S | L | GI 2612939 | | | | | | | | | | | | | | |

FIGURE 1D

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| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|-----|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---------|-----------|-----------|
| 1 | M | L | V | H | L | F | R | V | G | I | R | G | G | P | F | P | G | R | L | L | P | P | L | R | F | Q | T | F | S | A | 2274290 | |
| 1 | M | F | S | A | L | C | R | R | G | - | - | - | - | - | F | L | T | N | K | V | S | Q | F | R | - | S | T | Y | K | C | GI 425474 | |
| 31 | V | R | Y | S | D | G | Y | R | S | S | S | L | L | R | A | V | A | H | L | R | S | Q | L | W | A | H | L | P | R | A | 2274290 | |
| 25 | D | H | Y | N | L | K | T | H | I | K | P | L | - | K | C | S | S | S | L | R | L | T | V | G | T | G | L | - | F | I | GI 425474 | |
| 61 | P | L | A | P | R | W | S | P | S | A | W | C | W | V | G | G | A | L | L | G | P | M | V | L | S | K | H | P | H | L | 2274290 | |
| 53 | A | L | H | S | K | I | S | P | E | S | R | I | - | - | - | - | - | - | - | - | - | - | - | - | - | - | Q | T | V | Q | GI 425474 | |
| 91 | C | L | V | A | L | C | E | A | E | E | A | - | - | P | P | A | S | S | T | P | H | V | V | G | S | R | F | N | W | K | 2274290 | |
| 69 | C | E | V | D | S | Y | Q | T | D | Q | I | T | F | A | K | S | G | G | I | P | R | Y | I | G | V | - | - | - | - | - | GI 425474 | |
| 119 | L | F | W | Q | F | L | H | P | H | L | L | V | L | G | V | A | V | V | L | A | L | G | A | A | L | V | N | V | Q | I | 2274290 | |
| 94 | - | - | - | - | - | L | I | L | P | D | C | V | Y | L | F | G | A | I | L | G | A | F | V | A | A | V | M | N | V | Y | I | GI 425474 |
| 149 | P | L | L | G | Q | L | V | E | V | V | A | K | Y | T | R | D | H | V | G | S | F | M | T | E | S | Q | N | L | S | 2274290 | | |
| 120 | P | L | Y | L | G | D | F | V | S | S | L | S | R | C | V | V | T | H | E | G | - | F | V | S | A | V | Y | V | P | T | GI 425474 | |
| 179 | T | H | L | L | I | L | Y | G | V | Q | G | L | L | T | F | G | Y | L | V | L | L | S | H | V | G | E | R | M | A | V | 2274290 | |
| 149 | L | R | L | C | S | S | Y | L | L | Q | S | L | S | T | F | L | Y | I | G | L | L | G | S | V | G | E | R | M | A | R | GI 425474 | |

FIGURE 2A

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| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|-----|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---------|-----------|
| 209 | D | M | R | R | A | L | F | S | S | L | L | R | Q | D | I | T | F | F | D | A | N | K | T | G | Q | L | V | S | R | L | 2274290 |
| 179 | R | M | R | I | Q | L | F | R | K | L | V | Y | Q | D | V | A | Y | F | D | V | H | S | S | G | K | L | V | E | I | I | GI 425474 |
| 239 | T | T | D | V | Q | E | F | K | S | S | F | K | L | V | I | S | Q | G | L | R | S | C | T | Q | V | A | G | C | L | V | 2274290 |
| 209 | G | S | D | V | Q | N | F | K | S | S | F | K | Q | C | I | S | Q | G | L | R | N | G | I | Q | V | V | G | S | V | F | GI 425474 |
| 269 | S | L | S | M | L | S | T | R | L | T | L | L | M | V | A | T | P | A | L | M | G | V | G | T | L | M | G | S | G | 2274290 | |
| 239 | A | L | L | S | I | S | P | T | L | T | A | A | L | I | G | C | L | P | C | V | F | L | I | G | S | L | M | G | T | E | GI 425474 |
| 299 | L | R | K | L | S | R | Q | C | Q | E | Q | I | A | R | A | M | G | V | A | D | E | A | L | G | N | V | R | T | V | R | 2274290 |
| 269 | L | R | H | I | S | R | E | V | Q | S | Q | N | S | L | F | A | S | L | I | D | E | A | F | S | H | I | R | T | V | K | GI 425474 |
| 329 | A | F | A | M | E | Q | R | E | E | R | Y | G | A | E | L | E | A | C | R | C | R | A | E | E | L | G | R | G | I | 2274290 | |
| 299 | S | L | A | M | E | D | F | L | I | N | K | I | N | Y | N | V | D | K | A | K | M | L | S | E | K | L | S | F | G | I | GI 425474 |
| 359 | A | L | F | Q | G | L | S | N | I | A | F | N | C | M | V | L | G | T | L | F | I | G | G | S | L | V | A | G | Q | Q | 2274290 |
| 329 | G | S | F | Q | G | L | S | N | L | T | L | N | G | V | V | L | G | V | L | Y | V | G | G | H | L | M | S | R | G | E | GI 425474 |

FIGURE 2B

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| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|-----|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|-----------|-----------|---------|
| 389 | L | T | G | G | D | L | M | S | F | L | V | A | S | Q | T | V | Q | R | S | M | A | N | L | S | V | L | F | G | Q | V | 2274290 | |
| 359 | L | D | A | G | H | L | M | S | F | L | A | T | T | Q | T | L | Q | R | S | L | T | Q | L | S | L | L | Y | G | Q | V | GI 425474 | |
| 419 | V | R | G | L | S | A | G | A | R | V | F | E | Y | M | A | L | N | P | - | - | - | - | C | I | P | L | S | G | G | C | - | 2274290 |
| 389 | V | R | G | Y | T | A | L | K | R | I | H | D | I | L | A | L | P | S | G | I | G | S | I | P | S | S | S | S | S | L | GI 425474 | |
| 445 | C | V | P | K | E | Q | L | R | G | - | - | - | - | - | - | - | - | - | - | - | - | S | V | T | F | Q | N | V | C | 2274290 | | |
| 419 | V | V | S | K | Q | H | V | N | N | I | K | E | L | P | S | S | S | I | Y | S | A | P | S | I | E | F | S | D | V | K | GI 425474 | |
| 462 | F | S | Y | P | C | R | P | G | F | E | V | L | K | D | F | T | L | T | L | P | P | G | K | I | V | A | L | V | G | Q | 2274290 | |
| 449 | F | A | Y | P | N | R | P | E | T | I | V | L | N | E | L | S | M | F | L | P | G | K | V | I | A | L | V | G | Q | GI 425474 | | |
| 492 | S | G | G | K | T | T | V | A | S | L | L | E | R | F | Y | D | P | T | A | G | V | V | M | L | D | G | R | D | L | 2274290 | | |
| 479 | S | G | A | G | K | S | T | V | V | S | L | L | E | R | F | Y | D | P | I | S | G | E | I | L | L | N | G | D | K | L | GI 425474 | |
| 522 | R | T | L | D | P | S | W | L | R | G | Q | V | V | G | F | I | S | Q | E | P | V | L | F | G | T | I | M | E | N | 2274290 | | |
| 509 | T | N | F | N | V | N | Y | L | R | S | K | L | I | G | Y | I | S | Q | E | P | Q | I | F | N | A | S | I | R | E | N | GI 425474 | |

FIGURE 2C

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| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|-----|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|-----------|---|---------|---|---|---|---|---|---|---|---------|-----------|
| 552 | I | R | F | G | K | L | E | A | S | D | E | E | V | Y | T | A | A | R | E | A | N | A | H | E | F | I | T | S | - | F | 2274290 |
| 539 | I | R | F | G | R | F | D | A | T | D | E | E | V | E | E | A | A | K | L | A | Y | A | H | D | F | I | S | N | D | L | GI 425474 |
| 581 | P | E | G | Y | N | T | V | V | G | E | R | G | T | - | - | - | L | S | G | G | Q | K | Q | R | L | A | I | A | R | 2274290 | |
| 569 | P | Y | G | Y | D | T | L | V | G | Q | G | T | G | T | I | A | G | L | S | G | G | Q | R | Q | R | I | A | I | A | R | GI 425474 |
| 608 | A | L | I | K | Q | P | T | V | L | I | L | D | E | A | T | S | A | L | D | A | E | S | E | R | V | V | Q | E | A | L | 2274290 |
| 599 | I | L | L | K | N | A | P | I | L | L | M | D | E | A | T | S | A | L | D | T | E | S | E | A | K | V | Q | N | A | L | GI 425474 |
| 638 | D | R | A | S | A | G | R | T | V | L | V | I | A | H | R | L | S | T | V | R | G | A | H | C | I | V | V | M | A | D | 2274290 |
| 629 | N | N | A | M | K | G | R | T | V | L | I | I | A | H | R | L | S | T | V | R | K | A | D | L | I | L | V | M | S | K | GI 425474 |
| 668 | G | R | V | W | E | A | G | T | H | E | E | L | L | K | K | G | G | L | Y | A | E | L | I | R | R | Q | A | L | D | A | 2274290 |
| 659 | G | Q | I | V | E | K | G | T | H | S | E | L | M | A | N | H | G | Y | Y | N | L | V | Q | R | Q | - | - | - | - | - | GI 425474 |
| 698 | P | R | T | A | A | P | P | P | K | K | P | E | G | P | R | S | H | Q | H | K | S | 2274290 | | | | | | | | | |
| 685 | - | - | - | - | - | - | - | - | - | - | - | - | E | G | C | D | V | F | D | GI 425474 | | | | | | | | | | | |

FIGURE 2D

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| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|-----|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|------------|------------|
| 1 | M | S | V | G | V | S | T | S | A | P | L | S | P | T | S | G | T | S | V | G | M | S | T | F | S | I | M | D | Y | V | 2740029 |
| 1 | M | T | V | A | - | S | T | A | A | P | S | Y | T | T | S | D | T | N | R | V | I | S | T | F | S | V | V | D | Y | V | GI 3015617 |
| 31 | V | F | V | L | L | V | L | S | L | A | I | G | L | Y | H | A | C | R | G | W | G | R | H | T | V | G | E | L | L | 2740029 | |
| 30 | V | F | G | L | L | V | L | S | L | V | I | G | L | Y | H | A | C | R | G | W | G | R | H | T | V | G | E | L | L | GI 3015617 | |
| 61 | M | A | D | R | K | M | G | C | L | P | V | A | L | S | L | L | A | T | F | Q | S | A | V | A | I | L | G | V | P | S | 2740029 |
| 60 | M | A | D | R | K | M | G | C | L | P | V | A | L | S | L | L | A | T | F | Q | S | A | V | A | I | L | G | P | A | GI 3015617 | |
| 91 | E | I | Y | R | F | G | T | Q | Y | W | F | L | G | C | C | Y | F | L | G | L | L | I | P | A | H | I | F | I | P | V | 2740029 |
| 90 | E | I | Y | R | F | G | T | Q | Y | W | F | L | G | C | S | Y | F | L | G | L | L | I | P | A | H | I | F | I | P | V | GI 3015617 |
| 121 | F | Y | R | L | H | L | T | S | A | Y | E | Y | L | E | L | R | F | N | K | T | V | R | V | C | G | T | V | T | F | I | 2740029 |
| 120 | F | Y | R | L | H | L | T | S | A | Y | E | Y | L | E | L | R | F | N | K | A | V | R | I | C | G | T | V | T | F | I | GI 3015617 |
| 151 | F | Q | M | V | I | Y | M | G | V | V | L | Y | A | P | S | L | A | L | N | A | V | T | G | F | D | L | W | L | S | V | 2740029 |
| 150 | F | Q | M | V | V | Y | M | G | V | A | L | Y | A | P | S | L | A | L | N | A | V | T | G | F | D | L | W | L | S | V | GI 3015617 |

FIGURE 3A

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| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|-----|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|------------|
| 181 | L | A | L | G | I | V | C | T | V | Y | T | A | L | G | G | L | K | A | V | I | W | T | D | V | F | Q | T | L | V | M | 2740029 |
| 180 | L | A | L | G | I | V | C | N | I | Y | T | A | L | G | G | L | K | A | V | I | W | T | D | V | F | Q | T | L | I | M | GI 3015617 |
| 211 | F | L | G | Q | L | A | V | I | I | V | G | S | A | K | V | G | G | L | G | R | V | W | A | V | A | S | Q | H | G | R | 2740029 |
| 210 | F | L | G | Q | L | V | V | I | I | V | G | A | A | K | V | G | G | L | G | H | V | W | A | V | A | S | Q | H | G | L | GI 3015617 |
| 241 | I | S | G | F | E | L | D | P | D | P | F | V | R | H | T | F | W | T | L | A | F | G | G | V | F | M | M | L | S | L | 2740029 |
| 240 | I | S | G | I | E | L | D | P | D | P | F | V | R | H | T | F | W | T | L | A | F | G | G | V | F | M | M | L | S | L | GI 3015617 |
| 271 | Y | G | V | N | Q | A | Q | V | Q | R | Y | L | S | S | R | T | E | K | A | A | V | L | S | C | Y | A | V | F | P | F | 2740029 |
| 270 | Y | G | V | N | Q | A | Q | V | Q | R | Y | L | S | S | H | S | E | K | A | A | V | L | S | C | Y | A | V | F | P | C | GI 3015617 |
| 301 | Q | Q | V | S | L | C | V | G | C | L | I | G | L | V | M | F | A | Y | Y | Q | E | Y | P | M | S | I | Q | Q | A | Q | 2740029 |
| 300 | Q | Q | V | A | L | C | M | S | C | L | I | G | L | V | M | F | A | Y | Y | K | K | Y | S | M | S | P | Q | Q | E | Q | GI 3015617 |
| 331 | A | A | P | D | Q | F | V | L | Y | F | V | M | D | L | L | K | G | L | P | G | L | P | G | L | F | I | A | C | L | F | 2740029 |
| 330 | A | A | P | D | Q | L | V | L | Y | F | V | M | D | L | L | K | D | M | P | G | L | P | G | L | F | V | A | C | L | F | GI 3015617 |

FIGURE 3B

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| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|-----|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|------------|
| 361 | S | G | S | L | S | T | I | S | S | A | F | N | S | L | A | T | V | T | M | E | D | L | I | R | P | W | F | P | E | F | 2740029 |
| 360 | S | G | S | L | S | T | I | S | S | A | F | N | S | L | A | T | V | T | M | E | D | L | I | Q | P | W | F | P | Q | L | GI 3015617 |
| 391 | S | E | A | R | A | I | M | L | S | R | G | L | A | F | G | Y | G | L | L | C | L | G | M | A | Y | I | S | S | Q | M | 2740029 |
| 390 | T | E | T | R | A | I | M | L | S | R | S | L | A | F | A | Y | G | L | V | C | L | G | M | A | Y | V | S | S | H | L | GI 3015617 |
| 421 | G | P | V | L | Q | A | A | I | S | I | F | G | M | V | G | G | P | L | L | G | L | F | C | L | G | M | F | F | P | C | 2740029 |
| 420 | G | S | V | L | Q | A | A | L | S | I | F | G | M | V | G | G | P | L | L | G | L | F | C | L | G | M | F | F | P | C | GI 3015617 |
| 451 | A | N | P | P | G | A | V | V | G | L | L | A | G | L | V | M | A | F | W | I | G | I | G | S | I | V | T | S | M | G | 2740029 |
| 450 | A | N | P | L | G | A | I | V | G | L | L | T | G | L | T | M | A | F | W | I | G | I | G | S | I | V | S | R | M | S | GI 3015617 |
| 481 | S | S | M | P | P | S | P | S | N | G | S | S | F | S | L | P | T | N | L | T | V | A | T | V | T | T | L | M | P | L | 2740029 |
| 480 | S | A | A | A | S | P | P | L | N | G | S | S | S | F | L | P | S | N | L | T | V | A | T | V | T | T | L | M | P | - | GI 3015617 |
| 511 | T | T | F | S | K | P | T | G | L | Q | R | F | Y | S | L | S | Y | L | W | Y | S | A | H | N | S | T | T | V | I | V | 2740029 |
| 509 | S | T | L | S | K | P | T | G | L | Q | Q | F | Y | S | L | S | Y | L | W | Y | S | A | H | N | S | T | T | V | I | A | GI 3015617 |

FIGURE 3C

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| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|-----|---|---|---|---|---|---|---|------------|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---------|------------|
| 541 | V | G | L | I | V | S | L | L | T | G | R | M | R | G | R | S | L | N | P | A | T | I | Y | P | V | L | P | K | L | L | 2740029 |
| 539 | V | G | L | I | V | S | L | L | T | G | R | M | R | G | R | S | L | N | P | G | T | I | Y | P | V | L | P | K | L | L | GI 3015617 |
| 571 | S | L | L | P | L | S | C | Q | K | R | L | H | C | - | R | S | Y | G | Q | D | - | H | L | D | T | G | L | F | P | E | 2740029 |
| 569 | A | L | L | P | L | S | C | Q | K | R | L | - | C | W | R | S | H | N | Q | D | I | P | V | V | T | N | L | F | P | E | GI 3015617 |
| 599 | K | P | R | N | G | V | L | G | D | S | R | D | K | E | A | M | A | L | D | G | T | A | Y | Q | G | S | S | T | C | 2740029 | |
| 598 | K | M | G | N | G | A | L | Q | D | S | R | D | K | E | R | M | A | E | D | G | L | V | H | Q | P | C | S | P | T | Y | GI 3015617 |
| 629 | I | L | Q | E | T | S | L | 2740029 | | | | | | | | | | | | | | | | | | | | | | | |
| 628 | I | V | Q | E | T | S | L | GI 3015617 | | | | | | | | | | | | | | | | | | | | | | | |

FIGURE 3D

SEQUENCE LISTING

<110> INCYTE PHARMACEUTICALS, INC.
 HILLMAN, Jennifer L.
 YUE, Henry
 TANG, Y. Tom
 LAL, Preeti
 CORLEY, Neil C.
 GUEGLER, Karl J.
 BAUGHN, Mariah R.
 AZIMZAI, Yalda
 LU, Dyung Aina M.

<120> MEMBRANE TRANSPORT PROTEINS

<130> PF-0633 PCT

<140> To Be Assigned

<141> Herewith

<150> 09/186,778; unassigned; 09/200,277; unassigned; 09/221,405;
 unassigned; 60/121,896

<151> 1998-11-04; 1998-11-04; 1998-11-24; 1998-11-24; 1998-12-22;
 1998-12-22; 1999-02-26

<160> 43

<170> PERL Program

<210> 1

<211> 384

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 961344CD1

<400> 1

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|
| Met | Leu | Thr | Gly | Asp | Lys | Leu | Glu | Thr | Ala | Thr | Cys | Ile | Ala | Lys | |
| | | | | | | | | | | | | | | | |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |
| Ser | Ser | His | Leu | Val | Ser | Arg | Thr | Gln | Asp | Ile | His | Ile | Phe | Arg | |
| | | | | 20 | | | | | 25 | | | | | 30 | |
| Gln | Val | Thr | Ser | Arg | Gly | Glu | Ala | His | Leu | Glu | Leu | Asn | Ala | Phe | |
| | | | | 35 | | | | | 40 | | | | | 45 | |
| Arg | Arg | Lys | His | Asp | Cys | Ala | Leu | Val | Ile | Ser | Gly | Asp | Ser | Leu | |
| | | | | 50 | | | | | 55 | | | | | 60 | |
| Glu | Val | Cys | Leu | Lys | Tyr | Tyr | Glu | His | Glu | Phe | Val | Glu | Leu | Ala | |
| | | | | 65 | | | | | 70 | | | | | 75 | |
| Cys | Gln | Cys | Pro | Ala | Val | Val | Cys | Cys | Arg | Cys | Ser | Pro | Thr | Gln | |
| | | | | 80 | | | | | 85 | | | | | 90 | |
| Lys | Ala | Arg | Ile | Val | Thr | Leu | Leu | Gln | Gln | His | Thr | Gly | Arg | Arg | |
| | | | | 95 | | | | | 100 | | | | | 105 | |

WO 00/26245

Thr Cys Ala Ile Gly Asp Gly Gly Asn Asp Val Ser Met Ile Gln
 110 115 120
 Ala Ala Asp Cys Gly Ile Gly Ile Glu Gly Lys Glu Gly Lys Gln
 125 130 135
 Ala Ser Leu Ala Ala Asp Phe Ser Ile Thr Gln Phe Arg His Ile
 140 145 150
 Gly Arg Leu Leu Met Val His Gly Arg Asn Ser Tyr Lys Arg Ser
 155 160 165
 Ala Ala Leu Gly Gln Phe Val Met His Arg Gly Leu Ile Ile Ser
 170 175 180
 Thr Met Gln Ala Val Phe Ser Ser Val Phe Tyr Phe Ala Ser Val
 185 190 195
 Pro Leu Tyr Gln Gly Phe Leu Met Val Gly Tyr Ala Thr Ile Tyr
 200 205 210
 Thr Met Phe Pro Val Phe Ser Leu Val Leu Asp Gln Asp Val Lys
 215 220 225
 Pro Glu Met Ala Met Leu Tyr Pro Glu Leu Tyr Lys Asp Leu Thr
 230 235 240
 Lys Gly Arg Ser Leu Ser Phe Lys Thr Phe Leu Ile Trp Val Leu
 245 250 255
 Ile Ser Ile Tyr Gln Gly Gly Ile Leu Met Tyr Gly Ala Leu Val
 260 265 270
 Leu Phe Glu Ser Glu Phe Val His Val Val Ala Ile Ser Phe Thr
 275 280 285
 Ala Leu Ile Leu Thr Glu Leu Leu Met Val Ala Leu Thr Val Arg
 290 295 300
 Thr Trp His Trp Leu Met Val Val Ala Glu Phe Leu Ser Leu Gly
 305 310 315
 Cys Tyr Val Ser Ser Leu Ala Phe Leu Asn Glu Tyr Phe Gly Ile
 320 325 330
 Gly Arg Val Ser Phe Gly Ala Phe Leu Asp Val Ala Phe Ile Thr
 335 340 345
 Thr Val Thr Phe Leu Trp Lys Val Ser Ala Ile Thr Val Val Ser
 350 355 360
 Cys Leu Pro Leu Tyr Val Leu Lys Tyr Leu Arg Arg Lys Leu Ser
 365 370 375
 Pro Pro Ser Tyr Cys Lys Leu Ala Ser
 380

<210> 2

<211> 846

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 3128782CD1

<400> 2

Met Pro Lys Ala Pro Lys Gln Gln Pro Pro Glu Pro Glu Trp Ile
 1 5 10 15
 Gly Asp Gly Glu Ser Thr Ser Pro Ser Asp Lys Val Val Lys Lys
 20 25 30
 Gly Lys Lys Asp Lys Lys Ile Lys Lys Thr Phe Phe Glu Glu Leu

| | | | |
|---|-----|-----|-----|
| | 35 | 40 | 45 |
| Ala Val Glu Asp Lys Gln Ala Gly Glu Glu Glu Lys Val Leu Lys | 50 | 55 | 60 |
| Glu Lys Glu Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln Lys | 65 | 70 | 75 |
| Lys Lys Arg Asp Thr Arg Lys Gly Arg Arg Lys Lys Asp Val Asp | 80 | 85 | 90 |
| Asp Asp Gly Glu Glu Lys Glu Leu Met Glu Arg Leu Lys Lys Leu | 95 | 100 | 105 |
| Ser Val Pro Thr Ser Asp Glu Glu Asp Glu Val Pro Ala Pro Lys | 110 | 115 | 120 |
| Pro Arg Gly Gly Lys Lys Thr Lys Gly Gly Asn Val Phe Ala Ala | 125 | 130 | 135 |
| Leu Ile Gln Asp Gln Ser Glu Glu Glu Glu Glu Glu Glu Lys His | 140 | 145 | 150 |
| Pro Pro Lys Pro Ala Lys Pro Glu Lys Asn Arg Ile Asn Lys Ala | 155 | 160 | 165 |
| Val Ser Glu Glu Gln Gln Pro Ala Leu Lys Gly Lys Lys Gly Lys | 170 | 175 | 180 |
| Glu Glu Lys Ser Lys Gly Lys Ala Lys Pro Gln Asn Lys Phe Ala | 185 | 190 | 195 |
| Ala Leu Asp Asn Glu Glu Glu Asp Lys Glu Glu Glu Ile Ile Lys | 200 | 205 | 210 |
| Glu Lys Glu Pro Pro Lys Gln Gly Lys Glu Lys Ala Lys Lys Ala | 215 | 220 | 225 |
| Glu Gln Gly Ser Glu Glu Glu Gly Glu Gly Glu Glu Glu Glu Glu | 230 | 235 | 240 |
| Glu Gly Gly Glu Ser Lys Ala Asp Asp Pro Tyr Ala His Leu Ser | 245 | 250 | 255 |
| Lys Lys Glu Lys Lys Lys Leu Lys Lys Gln Met Glu Tyr Glu Arg | 260 | 265 | 270 |
| Gln Val Ala Ser Leu Lys Ala Ala Asn Ala Ala Glu Asn Asp Phe | 275 | 280 | 285 |
| Ser Val Ser Gln Ala Glu Met Ser Ser Arg Gln Ala Met Leu Glu | 290 | 295 | 300 |
| Asn Ala Ser Asp Ile Lys Leu Glu Lys Phe Ser Ile Ser Ala His | 305 | 310 | 315 |
| Gly Lys Glu Leu Phe Val Asn Ala Asp Leu Tyr Ile Val Ala Gly | 320 | 325 | 330 |
| Arg Arg Tyr Gly Leu Val Gly Pro Asn Gly Lys Gly Lys Thr Thr | 335 | 340 | 345 |
| Leu Leu Lys His Ile Ala Asn Arg Ala Leu Ser Ile Pro Pro Asn | 350 | 355 | 360 |
| Ile Asp Val Leu Leu Cys Glu Gln Glu Val Val Ala Asp Glu Thr | 365 | 370 | 375 |
| Pro Ala Val Gln Ala Val Leu Arg Ala Asp Thr Lys Arg Leu Lys | 380 | 385 | 390 |
| Leu Leu Glu Glu Glu Arg Arg Leu Gln Gly Gln Leu Glu Gln Gly | 395 | 400 | 405 |
| Asp Asp Thr Ala Ala Glu Arg Leu Glu Lys Val Tyr Glu Glu Leu | 410 | 415 | 420 |
| Arg Ala Thr Gly Ala Ala Ala Ala Glu Ala Lys Ala Arg Arg Ile | 425 | 430 | 435 |
| Leu Ala Gly Leu Gly Phe Asp Pro Glu Met Gln Asn Arg Pro Thr | 440 | 445 | 450 |

WO 00/26245

| | | | |
|---|-----|-----|-----|
| Gln Lys Phe Ser Gly Gly Trp Arg Met Arg Val Ser Leu Ala Arg | 455 | 460 | 465 |
| Ala Leu Phe Met Glu Pro Thr Leu Leu Met Leu Asp Glu Pro Thr | 470 | 475 | 480 |
| Asn His Leu Asp Leu Asn Ala Val Ile Trp Leu Asn Asn Tyr Leu | 485 | 490 | 495 |
| Gln Gly Trp Arg Lys Thr Leu Leu Ile Val Ser His Asp Gln Gly | 500 | 505 | 510 |
| Phe Leu Asp Asp Val Cys Thr Asp Ile Ile His Leu Asp Ala Gln | 515 | 520 | 525 |
| Arg Leu His Tyr Tyr Arg Gly Asn Tyr Met Thr Phe Lys Lys Met | 530 | 535 | 540 |
| Tyr Gln Gln Lys Gln Lys Glu Leu Leu Lys Gln Tyr Glu Lys Gln | 545 | 550 | 555 |
| Glu Lys Lys Leu Lys Glu Leu Lys Ala Gly Gly Lys Ser Thr Lys | 560 | 565 | 570 |
| Gln Ala Glu Lys Gln Thr Lys Glu Ala Leu Thr Arg Lys Gln Gln | 575 | 580 | 585 |
| Lys Cys Arg Arg Lys Asn Gln Asp Glu Glu Ser Gln Glu Ala Pro | 590 | 595 | 600 |
| Glu Leu Leu Lys Arg Pro Lys Glu Tyr Thr Val Arg Phe Thr Phe | 605 | 610 | 615 |
| Pro Asp Pro Pro Pro Leu Ser Pro Pro Val Leu Gly Leu His Gly | 620 | 625 | 630 |
| Val Thr Phe Gly Tyr Gln Gly Gln Lys Pro Leu Phe Lys Asn Leu | 635 | 640 | 645 |
| Asp Phe Gly Ile Asp Met Asp Ser Arg Ile Cys Ile Val Gly Pro | 650 | 655 | 660 |
| Asn Gly Val Gly Lys Ser Thr Leu Leu Leu Leu Leu Thr Gly Lys | 665 | 670 | 675 |
| Leu Thr Pro Thr His Gly Glu Met Arg Lys Asn His Arg Leu Lys | 680 | 685 | 690 |
| Ile Gly Phe Phe Asn Gln Gln Tyr Ala Glu Gln Leu Arg Met Glu | 695 | 700 | 705 |
| Glu Thr Pro Thr Glu Tyr Leu Gln Arg Gly Phe Asn Leu Pro Tyr | 710 | 715 | 720 |
| Gln Asp Ala Arg Lys Cys Leu Gly Arg Phe Gly Leu Glu Ser His | 725 | 730 | 735 |
| Ala His Thr Ile Gln Ile Cys Lys Leu Ser Gly Gly Gln Lys Ala | 740 | 745 | 750 |
| Arg Val Val Phe Ala Glu Leu Ala Cys Arg Glu Pro Asp Val Leu | 755 | 760 | 765 |
| Ile Leu Asp Glu Pro Thr Asn Asn Leu Asp Ile Glu Ser Ile Asp | 770 | 775 | 780 |
| Ala Leu Gly Glu Ala Ile Asn Glu Tyr Lys Gly Ala Val Ile Val | 785 | 790 | 795 |
| Val Ser His Asp Ala Arg Leu Ile Thr Glu Thr Asn Cys Gln Leu | 800 | 805 | 810 |
| Trp Val Val Glu Glu Gln Ser Val Ser Gln Ile Asp Gly Asp Phe | 815 | 820 | 825 |
| Glu Asp Tyr Lys Arg Glu Val Leu Glu Ala Leu Gly Glu Val Met | 830 | 835 | 840 |
| Val Ser Arg Pro Arg Glu | 845 | | |

WO 00/26245

<210> 3
 <211> 511
 <212> PRT
 <213> Homo sapiens

<220>
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 <223> Incyte ID No: 1720440CD1

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 1 5 10 15
 Lys Leu Gly Val Glu Ala Ala Leu Ile Asn Thr Asn Leu Arg Arg
 20 25 30
 Asp Ala Leu Leu His Cys Leu Thr Thr Ser Arg Ala Arg Ala Leu
 35 40 45
 Val Phe Gly Ser Glu Met Ala Ser Ala Ile Cys Glu Val His Ala
 50 55 60
 Ser Leu Asp Pro Ser Leu Ser Leu Phe Cys Ser Gly Ser Trp Glu
 65 70 75
 Pro Gly Ala Val Pro Pro Ser Thr Glu His Leu Asp Pro Leu Leu
 80 85 90
 Lys Asp Ala Pro Lys His Leu Pro Ser Cys Pro Asp Lys Gly Phe
 95 100 105
 Thr Asp Lys Leu Phe Tyr Ile Tyr Thr Ser Gly Thr Thr Gly Leu
 110 115 120
 Pro Lys Ala Ala Ile Val Val His Ser Arg Tyr Tyr Arg Met Ala
 125 130 135
 Ala Leu Val Tyr Tyr Gly Phe Arg Met Arg Pro Asn Asp Ile Val
 140 145 150
 Tyr Asp Cys Leu Pro Leu Tyr His Ser Ala Gly Asn Ile Val Gly
 155 160 165
 Ile Gly Gln Cys Leu Leu His Gly Met Thr Val Val Ile Arg Lys
 170 175 180
 Lys Phe Ser Ala Ser Arg Phe Trp Asp Asp Cys Ile Lys Tyr Asn
 185 190 195
 Cys Thr Ile Val Gln Tyr Ile Gly Glu Leu Cys Arg Tyr Leu Leu
 200 205 210
 Asn Gln Pro Pro Arg Glu Ala Glu Asn Gln His Gln Val Arg Met
 215 220 225
 Ala Leu Gly Asn Gly Leu Arg Gln Ser Ile Trp Thr Asn Phe Ser
 230 235 240
 Ser Arg Phe His Ile Pro Gln Val Ala Glu Phe Tyr Gly Ala Thr
 245 250 255
 Glu Cys Asn Cys Ser Leu Gly Asn Phe Asp Ser Gln Val Gly Ala
 260 265 270
 Cys Gly Phe Asn Ser Arg Ile Leu Ser Ser Val Tyr Pro Ile Arg
 275 280 285
 Leu Val Arg Val Asn Glu Asp Thr Met Glu Leu Ile Arg Gly Pro
 290 295 300
 Asp Gly Val Cys Ile Pro Cys Gln Pro Gly Glu Pro Gly Gln Leu
 305 310 315
 Val Gly Arg Ile Ile Gln Lys Asp Pro Leu Arg Arg Phe Asp Gly
 320 325 330
 Tyr Leu Asn Gln Gly Ala Asn Asn Lys Lys Ile Ala Lys Asp Val

WO 00/26245

| | | | |
|---|-----|-----|-----|
| | 335 | 340 | 345 |
| Phe Lys Lys Gly Asp Gln Ala Tyr Leu Thr Gly Asp Val Leu Val | | | |
| | 350 | 355 | 360 |
| Met Asp Glu Leu Gly Tyr Leu Tyr Phe Arg Asp Arg Thr Gly Asp | | | |
| | 365 | 370 | 375 |
| Thr Phe Arg Trp Lys Gly Glu Asn Val Ser Thr Thr Glu Val Glu | | | |
| | 380 | 385 | 390 |
| Gly Thr Leu Ser Arg Leu Leu Asp Met Ala Asp Val Ala Val Tyr | | | |
| | 395 | 400 | 405 |
| Gly Val Glu Val Pro Gly Thr Glu Gly Arg Ala Gly Met Ala Ala | | | |
| | 410 | 415 | 420 |
| Val Ala Ser Pro Thr Gly Asn Cys Asp Leu Glu Arg Phe Ala Gln | | | |
| | 425 | 430 | 435 |
| Val Leu Glu Lys Glu Leu Pro Leu Tyr Ala Arg Pro Ile Phe Leu | | | |
| | 440 | 445 | 450 |
| Arg Leu Leu Pro Glu Leu His Lys Thr Gly Thr Tyr Lys Phe Gln | | | |
| | 455 | 460 | 465 |
| Lys Thr Glu Leu Arg Lys Glu Gly Phe Asp Pro Ala Ile Val Lys | | | |
| | 470 | 475 | 480 |
| Asp Pro Leu Phe Tyr Leu Asp Ala Gln Lys Gly Arg Tyr Val Pro | | | |
| | 485 | 490 | 495 |
| Leu Asp Gln Glu Ala Tyr Ser Arg Ile Gln Ala Gly Glu Glu Lys | | | |
| | 500 | 505 | 510 |

Leu

<210> 4

<211> 718

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 2274290CD1

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|---|-----|-----|
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| 1 | 5 | 10 |
| Pro Gly Arg Leu Leu Pro Pro Leu Arg Phe Gln Thr Phe Ser Ala | | |
| | 20 | 25 |
| Val Arg Tyr Ser Asp Gly Tyr Arg Ser Ser Ser Leu Leu Arg Ala | | |
| | 35 | 40 |
| Val Ala His Leu Arg Ser Gln Leu Trp Ala His Leu Pro Arg Ala | | |
| | 50 | 55 |
| Pro Leu Ala Pro Arg Trp Ser Pro Ser Ala Trp Cys Trp Val Gly | | |
| | 65 | 70 |
| Gly Ala Leu Leu Gly Pro Met Val Leu Ser Lys His Pro His Leu | | |
| | 80 | 85 |
| Cys Leu Val Ala Leu Cys Glu Ala Glu Glu Ala Pro Pro Ala Ser | | |
| | 95 | 100 |
| Ser Thr Pro His Val Val Gly Ser Arg Phe Asn Trp Lys Leu Phe | | |
| | 110 | 115 |
| Trp Gln Phe Leu His Pro His Leu Leu Val Leu Gly Val Ala Val | | |
| | 125 | 130 |
| Val Leu Ala Leu Gly Ala Ala Leu Val Asn Val Gln Ile Pro Leu | | |

WO 00/26245

| | | | |
|-------------------------------------|-------------------------|-----|-----|
| | 140 | 145 | 150 |
| Leu Leu Gly Gln Leu Val Glu Val Val | Ala Lys Tyr Thr Arg Asp | | |
| | 155 | 160 | 165 |
| His Val Gly Ser Phe Met Thr Glu Ser | Gln Asn Leu Ser Thr His | | |
| | 170 | 175 | 180 |
| Leu Leu Ile Leu Tyr Gly Val Gln Gly | Leu Leu Thr Phe Gly Tyr | | |
| | 185 | 190 | 195 |
| Leu Val Leu Leu Ser His Val Gly Glu | Arg Met Ala Val Asp Met | | |
| | 200 | 205 | 210 |
| Arg Arg Ala Leu Phe Ser Ser Leu Leu | Arg Gln Asp Ile Thr Phe | | |
| | 215 | 220 | 225 |
| Phe Asp Ala Asn Lys Thr Gly Gln Leu | Val Ser Arg Leu Thr Thr | | |
| | 230 | 235 | 240 |
| Asp Val Gln Glu Phe Lys Ser Ser Phe | Lys Leu Val Ile Ser Gln | | |
| | 245 | 250 | 255 |
| Gly Leu Arg Ser Cys Thr Gln Val Ala | Gly Cys Leu Val Ser Leu | | |
| | 260 | 265 | 270 |
| Ser Met Leu Ser Thr Arg Leu Thr Leu | Leu Leu Met Val Ala Thr | | |
| | 275 | 280 | 285 |
| Pro Ala Leu Met Gly Val Gly Thr Leu | Met Gly Ser Gly Leu Arg | | |
| | 290 | 295 | 300 |
| Lys Leu Ser Arg Gln Cys Gln Glu Gln | Ile Ala Arg Ala Met Gly | | |
| | 305 | 310 | 315 |
| Val Ala Asp Glu Ala Leu Gly Asn Val | Arg Thr Val Arg Ala Phe | | |
| | 320 | 325 | 330 |
| Ala Met Glu Gln Arg Glu Glu Glu Arg | Tyr Gly Ala Glu Leu Glu | | |
| | 335 | 340 | 345 |
| Ala Cys Arg Cys Arg Ala Glu Glu Leu | Gly Arg Gly Ile Ala Leu | | |
| | 350 | 355 | 360 |
| Phe Gln Gly Leu Ser Asn Ile Ala Phe | Asn Cys Met Val Leu Gly | | |
| | 365 | 370 | 375 |
| Thr Leu Phe Ile Gly Gly Ser Leu Val | Ala Gly Gln Gln Leu Thr | | |
| | 380 | 385 | 390 |
| Gly Gly Asp Leu Met Ser Phe Leu Val | Ala Ser Gln Thr Val Gln | | |
| | 395 | 400 | 405 |
| Arg Ser Met Ala Asn Leu Ser Val Leu | Phe Gly Gln Val Val Arg | | |
| | 410 | 415 | 420 |
| Gly Leu Ser Ala Gly Ala Arg Val Phe | Glu Tyr Met Ala Leu Asn | | |
| | 425 | 430 | 435 |
| Pro Cys Ile Pro Leu Ser Gly Gly Cys | Cys Val Pro Lys Glu Gln | | |
| | 440 | 445 | 450 |
| Leu Arg Gly Ser Val Thr Phe Gln Asn | Val Cys Phe Ser Tyr Pro | | |
| | 455 | 460 | 465 |
| Cys Arg Pro Gly Phe Glu Val Leu Lys | Asp Phe Thr Leu Thr Leu | | |
| | 470 | 475 | 480 |
| Pro Pro Gly Lys Ile Val Ala Leu Val | Gly Gln Ser Gly Gly Gly | | |
| | 485 | 490 | 495 |
| Lys Thr Thr Val Ala Ser Leu Leu Glu | Arg Phe Tyr Asp Pro Thr | | |
| | 500 | 505 | 510 |
| Ala Gly Val Val Met Leu Asp Gly Arg | Asp Leu Arg Thr Leu Asp | | |
| | 515 | 520 | 525 |
| Pro Ser Trp Leu Arg Gly Gln Val Val | Gly Phe Ile Ser Gln Glu | | |
| | 530 | 535 | 540 |
| Pro Val Leu Phe Gly Thr Thr Ile Met | Glu Asn Ile Arg Phe Gly | | |
| | 545 | 550 | 555 |

WO 00/26245

Lys Leu Glu Ala Ser Asp Glu Glu Val Tyr Thr Ala Ala Arg Glu 570
 560 565
 Ala Asn Ala His Glu Phe Ile Thr Ser Phe Pro Glu Gly Tyr Asn 585
 575 580
 Thr Val Val Gly Glu Arg Gly Thr Thr Leu Ser Gly Gly Gln Lys 600
 590 595
 Gln Arg Leu Ala Ile Ala Arg Ala Leu Ile Lys Gln Pro Thr Val 615
 605 610
 Leu Ile Leu Asp Glu Ala Thr Ser Ala Leu Asp Ala Glu Ser Glu 630
 620 625
 Arg Val Val Gln Glu Ala Leu Asp Arg Ala Ser Ala Gly Arg Thr 645
 635 640
 Val Leu Val Ile Ala His Arg Leu Ser Thr Val Arg Gly Ala His 660
 650 655
 Cys Ile Val Val Met Ala Asp Gly Arg Val Trp Glu Ala Gly Thr 675
 665 670
 His Glu Glu Leu Leu Lys Lys Gly Gly Leu Tyr Ala Glu Leu Ile 690
 680 685
 Arg Arg Gln Ala Leu Asp Ala Pro Arg Thr Ala Ala Pro Pro Pro 705
 695 700
 Lys Lys Pro Glu Gly Pro Arg Ser His Gln His Lys Ser 715
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<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 2740029CD1

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 Gly Thr Ser Val Gly Met Ser Thr Phe Ser Ile Met Asp Tyr Val 30
 20 25
 Val Phe Val Leu Leu Leu Val Leu Ser Leu Ala Ile Gly Leu Tyr 45
 35 40
 His Ala Cys Arg Gly Trp Gly Arg His Thr Val Gly Glu Leu Leu 60
 50 55
 Met Ala Asp Arg Lys Met Gly Cys Leu Pro Val Ala Leu Ser Leu 75
 65 70
 Leu Ala Thr Phe Gln Ser Ala Val Ala Ile Leu Gly Val Pro Ser 90
 80 85
 Glu Ile Tyr Arg Phe Gly Thr Gln Tyr Trp Phe Leu Gly Cys Cys 105
 95 100
 Tyr Phe Leu Gly Leu Leu Ile Pro Ala His Ile Phe Ile Pro Val 120
 110 115
 Phe Tyr Arg Leu His Leu Thr Ser Ala Tyr Glu Tyr Leu Glu Leu 135
 125 130
 Arg Phe Asn Lys Thr Val Arg Val Cys Gly Thr Val Thr Phe Ile 150
 140 145
 Phe Gln Met Val Ile Tyr Met Gly Val Val Leu Tyr Ala Pro Ser

| | | | |
|---|-----|-----|-----|
| | 155 | 160 | 165 |
| Leu Ala Leu Asn Ala Val Thr Gly Phe Asp Leu Trp Leu Ser Val | | | |
| | 170 | 175 | 180 |
| Leu Ala Leu Gly Ile Val Cys Thr Val Tyr Thr Ala Leu Gly Gly | | | |
| | 185 | 190 | 195 |
| Leu Lys Ala Val Ile Trp Thr Asp Val Phe Gln Thr Leu Val Met | | | |
| | 200 | 205 | 210 |
| Phe Leu Gly Gln Leu Ala Val Ile Ile Val Gly Ser Ala Lys Val | | | |
| | 215 | 220 | 225 |
| Gly Gly Leu Gly Arg Val Trp Ala Val Ala Ser Gln His Gly Arg | | | |
| | 230 | 235 | 240 |
| Ile Ser Gly Phe Glu Leu Asp Pro Asp Pro Phe Val Arg His Thr | | | |
| | 245 | 250 | 255 |
| Phe Trp Thr Leu Ala Phe Gly Gly Val Phe Met Met Leu Ser Leu | | | |
| | 260 | 265 | 270 |
| Tyr Gly Val Asn Gln Ala Gln Val Gln Arg Tyr Leu Ser Ser Arg | | | |
| | 275 | 280 | 285 |
| Thr Glu Lys Ala Ala Val Leu Ser Cys Tyr Ala Val Phe Pro Phe | | | |
| | 290 | 295 | 300 |
| Gln Gln Val Ser Leu Cys Val Gly Cys Leu Ile Gly Leu Val Met | | | |
| | 305 | 310 | 315 |
| Phe Ala Tyr Tyr Gln Glu Tyr Pro Met Ser Ile Gln Gln Ala Gln | | | |
| | 320 | 325 | 330 |
| Ala Ala Pro Asp Gln Phe Val Leu Tyr Phe Val Met Asp Leu Leu | | | |
| | 335 | 340 | 345 |
| Lys Gly Leu Pro Gly Leu Pro Gly Leu Phe Ile Ala Cys Leu Phe | | | |
| | 350 | 355 | 360 |
| Ser Gly Ser Leu Ser Thr Ile Ser Ser Ala Phe Asn Ser Leu Ala | | | |
| | 365 | 370 | 375 |
| Thr Val Thr Met Glu Asp Leu Ile Arg Pro Trp Phe Pro Glu Phe | | | |
| | 380 | 385 | 390 |
| Ser Glu Ala Arg Ala Ile Met Leu Ser Arg Gly Leu Ala Phe Gly | | | |
| | 395 | 400 | 405 |
| Tyr Gly Leu Leu Cys Leu Gly Met Ala Tyr Ile Ser Ser Gln Met | | | |
| | 410 | 415 | 420 |
| Gly Pro Val Leu Gln Ala Ala Ile Ser Ile Phe Gly Met Val Gly | | | |
| | 425 | 430 | 435 |
| Gly Pro Leu Leu Gly Leu Phe Cys Leu Gly Met Phe Phe Pro Cys | | | |
| | 440 | 445 | 450 |
| Ala Asn Pro Pro Gly Ala Val Val Gly Leu Leu Ala Gly Leu Val | | | |
| | 455 | 460 | 465 |
| Met Ala Phe Trp Ile Gly Ile Gly Ser Ile Val Thr Ser Met Gly | | | |
| | 470 | 475 | 480 |
| Ser Ser Met Pro Pro Ser Pro Ser Asn Gly Ser Ser Phe Ser Leu | | | |
| | 485 | 490 | 495 |
| Pro Thr Asn Leu Thr Val Ala Thr Val Thr Thr Leu Met Pro Leu | | | |
| | 500 | 505 | 510 |
| Thr Thr Phe Ser Lys Pro Thr Gly Leu Gln Arg Phe Tyr Ser Leu | | | |
| | 515 | 520 | 525 |
| Ser Tyr Leu Trp Tyr Ser Ala His Asn Ser Thr Thr Val Ile Val | | | |
| | 530 | 535 | 540 |
| Val Gly Leu Ile Val Ser Leu Leu Thr Gly Arg Met Arg Gly Arg | | | |
| | 545 | 550 | 555 |
| Ser Leu Asn Pro Ala Thr Ile Tyr Pro Val Leu Pro Lys Leu Leu | | | |
| | 560 | 565 | 570 |

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<210> 6
<211> 535
<212> PRT
<213> Homo sapiens
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| <400> 6 | | | | | | | | | | | | | | |
|---------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Glu | Glu | Gly | Ala | Arg | His | Arg | Asn | Asn | Thr | Glu | Lys | Lys | His |
| 1 | | | | 5 | | | | | 10 | | | | | 15 |
| Pro | Gly | Gly | Gly | Glu | Ser | Asp | Ala | Ser | Pro | Glu | Ala | Gly | Ser | Gly |
| | | | | 20 | | | | | 25 | | | | | 30 |
| Gly | Gly | Gly | Val | Ala | Leu | Lys | Lys | Glu | Ile | Gly | Leu | Val | Ser | Ala |
| | | | | 35 | | | | | 40 | | | | | 45 |
| Cys | Gly | Ile | Ile | Val | Gly | Asn | Ile | Ile | Gly | Ser | Gly | Ile | Phe | Val |
| | | | | 50 | | | | | 55 | | | | | 60 |
| Ser | Pro | Lys | Gly | Val | Leu | Glu | Asn | Ala | Gly | Ser | Val | Gly | Leu | Ala |
| | | | | 65 | | | | | 70 | | | | | 75 |
| Leu | Ile | Val | Trp | Ile | Val | Thr | Gly | Phe | Ile | Thr | Val | Val | Gly | Ala |
| | | | | 80 | | | | | 85 | | | | | 90 |
| Leu | Cys | Tyr | Ala | Glu | Leu | Gly | Val | Thr | Ile | Pro | Lys | Ser | Gly | Gly |
| | | | | 95 | | | | | 100 | | | | | 105 |
| Asp | Tyr | Ser | Tyr | Val | Lys | Asp | Ile | Phe | Gly | Gly | Leu | Ala | Gly | Phe |
| | | | | 110 | | | | | 115 | | | | | 120 |
| Leu | Arg | Leu | Trp | Ile | Ala | Val | Leu | Val | Ile | Tyr | Pro | Thr | Asn | Gln |
| | | | | 125 | | | | | 130 | | | | | 135 |
| Ala | Val | Ile | Ala | Leu | Thr | Phe | Ser | Asn | Tyr | Val | Leu | Gln | Pro | Leu |
| | | | | 140 | | | | | 145 | | | | | 150 |
| Phe | Pro | Thr | Cys | Phe | Pro | Pro | Glu | Ser | Gly | Leu | Arg | Leu | Leu | Ala |
| | | | | 155 | | | | | 160 | | | | | 165 |
| Ala | Ile | Cys | Leu | Leu | Leu | Leu | Thr | Trp | Val | Asn | Cys | Ser | Ser | Val |
| | | | | 170 | | | | | 175 | | | | | 180 |
| Arg | Trp | Ala | Thr | Arg | Val | Gln | Asp | Ile | Phe | Thr | Ala | Gly | Lys | Leu |
| | | | | 185 | | | | | 190 | | | | | 195 |
| Leu | Ala | Leu | Ala | Leu | Ile | Ile | Ile | Met | Gly | Ile | Val | Gln | Ile | Cys |
| | | | | 200 | | | | | 205 | | | | | 210 |
| Lys | Gly | Glu | Tyr | Phe | Trp | Leu | Glu | Pro | Lys | Asn | Ala | Phe | Glu | Asn |
| | | | | 215 | | | | | 220 | | | | | 225 |
| Phe | Gln | Glu | Pro | Asp | Ile | Gly | Leu | Val | Ala | Leu | Ala | Phe | Leu | Gln |
| | | | | 230 | | | | | 235 | | | | | 240 |
| Gly | Ser | Phe | Ala | Tyr | Gly | Gly | Trp | Asn | Phe | Leu | Asn | Tyr | Val | Thr |

WO 00/26245

| | | | |
|---------------------|---------------------|---------------------|-----|
| | 245 | 250 | 255 |
| Glu Glu Leu Val Asp | Pro Tyr Lys Asn | Leu Pro Arg Ala Ile | Phe |
| | 260 | 265 | 270 |
| Ile Ser Ile Pro | Leu Val Thr Phe Val | Tyr Val Phe Ala Asn | Val |
| | 275 | 280 | 285 |
| Ala Tyr Val Thr | Ala Met Ser Pro Gln | Glu Leu Leu Ala Ser | Asn |
| | 290 | 295 | 300 |
| Ala Val Ala Val | Thr Phe Gly Glu Lys | Leu Leu Gly Val Met | Ala |
| | 305 | 310 | 315 |
| Trp Ile Met Pro | Ile Ser Val Ala Leu | Ser Thr Phe Gly Gly | Val |
| | 320 | 325 | 330 |
| Asn Gly Ser Leu | Phe Thr Ser Ser Arg | Leu Phe Phe Ala Gly | Ala |
| | 335 | 340 | 345 |
| Arg Glu Gly His | Leu Pro Ser Val Leu | Ala Met Ile His Val | Lys |
| | 350 | 355 | 360 |
| Arg Cys Thr Pro | Ile Pro Ala Leu Leu | Phe Thr Cys Ile Ser | Thr |
| | 365 | 370 | 375 |
| Leu Leu Met Leu | Val Thr Ser Asp Met | Tyr Thr Leu Ile Asn | Tyr |
| | 380 | 385 | 390 |
| Val Gly Phe Ile | Asn Tyr Leu Phe Tyr | Gly Val Thr Val Ala | Gly |
| | 395 | 400 | 405 |
| Gln Ile Val Leu | Arg Trp Lys Lys Pro | Asp Ile Pro Arg Pro | Ile |
| | 410 | 415 | 420 |
| Lys Ile Asn Leu | Leu Phe Pro Ile Ile | Tyr Leu Leu Phe Trp | Ala |
| | 425 | 430 | 435 |
| Phe Leu Leu Val | Phe Ser Leu Trp Ser | Glu Pro Val Val Cys | Gly |
| | 440 | 445 | 450 |
| Ile Gly Leu Ala | Ile Met Leu Thr Gly | Val Pro Val Tyr Phe | Leu |
| | 455 | 460 | 465 |
| Gly Val Tyr Trp | Gln His Lys Pro Lys | Cys Phe Ser Asp Phe | Ile |
| | 470 | 475 | 480 |
| Glu Leu Leu Thr | Leu Val Ser Gln Lys | Met Cys Val Val Val | Tyr |
| | 485 | 490 | 495 |
| Pro Glu Val Glu | Arg Gly Ser Gly Thr | Glu Glu Ala Asn Glu | Asp |
| | 500 | 505 | 510 |
| Met Glu Glu Gln | Gln Gln Pro Met Tyr | Gln Pro Thr Pro Thr | Lys |
| | 515 | 520 | 525 |
| Asp Lys Asp Val | Ala Gly Gln Pro Gln | Pro | |
| | 530 | 535 | |

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<211> 456

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 2466714CD1

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| | 10 | 15 |
| 1 | 5 | |
| Val Ser Val Gln Gln Pro Glu Glu Ala Glu Ala Glu Glu Leu Ser | | 30 |
| | 25 | |
| | 20 | |

WO 00/26245

| | | | |
|---|-----|-----|-----|
| Pro Leu Leu Ser Asn Glu Leu His Arg Gln Arg Ser Pro Gly Val | 35 | 40 | 45 |
| Ser Phe Gly Leu Ser Val Phe Asn Leu Met Asn Ala Ile Met Gly | 50 | 55 | 60 |
| Ser Gly Ile Leu Gly Leu Ala Tyr Val Met Ala Asn Thr Gly Val | 65 | 70 | 75 |
| Phe Gly Phe Ser Phe Leu Leu Leu Thr Val Ala Leu Leu Ala Ser | 80 | 85 | 90 |
| Tyr Ser Val His Leu Leu Leu Ser Met Cys Ile Gln Thr Ala Val | 95 | 100 | 105 |
| Thr Ser Tyr Glu Asp Leu Gly Leu Phe Ala Phe Gly Leu Pro Gly | 110 | 115 | 120 |
| Lys Leu Val Val Ala Gly Thr Ile Ile Ile Gln Asn Ile Gly Ala | 125 | 130 | 135 |
| Met Ser Ser Tyr Leu Leu Ile Ile Lys Thr Glu Leu Pro Ala Ala | 140 | 145 | 150 |
| Ile Ala Glu Phe Leu Thr Gly Asp Tyr Asn Arg Tyr Trp Tyr Leu | 155 | 160 | 165 |
| Asp Gly Gln Thr Leu Leu Ile Ile Ile Cys Val Gly Ile Val Phe | 170 | 175 | 180 |
| Pro Leu Ala Leu Leu Pro Lys Ile Gly Phe Leu Gly Tyr Thr Ser | 185 | 190 | 195 |
| Ser Leu Ser Phe Phe Phe Met Met Phe Phe Ala Leu Val Val Ile | 200 | 205 | 210 |
| Ile Lys Lys Trp Ser Ile Pro Cys Pro Leu Thr Leu Asn Tyr Val | 215 | 220 | 225 |
| Glu Lys Gly Phe Gln Ile Ser Asn Val Thr Asp Asp Cys Lys Pro | 230 | 235 | 240 |
| Lys Leu Phe His Phe Ser Lys Glu Ser Ala Tyr Ala Leu Pro Thr | 245 | 250 | 255 |
| Met Ala Phe Ser Phe Leu Cys His Thr Ser Ile Leu Pro Ile Tyr | 260 | 265 | 270 |
| Cys Glu Leu Gln Ser Pro Ser Lys Lys Arg Met Gln Asn Val Thr | 275 | 280 | 285 |
| Asn Thr Ala Ile Ala Leu Ser Phe Leu Ile Tyr Phe Ile Ser Ala | 290 | 295 | 300 |
| Leu Phe Gly Tyr Leu Thr Phe Tyr Asp Lys Val Glu Ser Glu Leu | 305 | 310 | 315 |
| Leu Lys Gly Tyr Ser Lys Tyr Leu Ser His Asp Val Val Val Met | 320 | 325 | 330 |
| Thr Val Lys Leu Cys Ile Leu Phe Ala Val Leu Leu Thr Val Pro | 335 | 340 | 345 |
| Leu Ile His Phe Pro Ala Arg Lys Ala Val Thr Met Met Phe Phe | 350 | 355 | 360 |
| Ser Asn Phe Pro Phe Ser Trp Ile Arg His Phe Leu Ile Thr Leu | 365 | 370 | 375 |
| Ala Leu Asn Ile Ile Ile Val Leu Leu Ala Ile Tyr Val Pro Asp | 380 | 385 | 390 |
| Ile Arg Asn Val Phe Gly Val Val Gly Ala Ser Thr Ser Thr Cys | 395 | 400 | 405 |
| Leu Ile Phe Ile Phe Pro Gly Leu Phe Tyr Leu Lys Leu Ser Arg | 410 | 415 | 420 |
| Glu Asp Phe Leu Ser Trp Lys Lys Leu Gly Ala Phe Val Leu Leu | 425 | 430 | 435 |
| Ile Phe Gly Ile Leu Val Gly Asn Phe Ser Leu Ala Leu Ile Ile | | | |

440
Phe Asp Trp Ile Asn Lys
455

445

450

<210> 8
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<212> PRT
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<220>
<221> misc_feature
<223> Incyte ID No: 2617942CD1

<400> 8
Met Phe Ala Asn Leu Lys Tyr Val Ser Leu Gly Ile Leu Val Phe
1 5 10 15
Gln Thr Thr Ser Leu Val Leu Thr Met Arg Tyr Ser Arg Thr Leu
20 25 30
Lys Glu Glu Gly Pro Arg Tyr Leu Ser Ser Thr Ala Val Val Val
35 40 45
Ala Glu Leu Leu Lys Ile Met Ala Cys Ile Leu Leu Val Tyr Lys
50 55 60
Asp Ser Lys Cys Ser Leu Arg Ala Leu Asn Arg Val Leu His Asp
65 70 75
Glu Ile Leu Asn Lys Pro Met Glu Thr Leu Lys Leu Ala Ile Pro
80 85 90
Ser Gly Ile Tyr Thr Leu Gln Asn Asn Leu Leu Tyr Val Ala Leu
95 100 105
Ser Asn Leu Asp Ala Ala Thr Tyr Gln Val Thr Tyr Gln Leu Lys
110 115 120
Ile Leu Thr Thr Ala Leu Phe Ser Val Ser Met Leu Ser Lys Lys
125 130 135
Leu Gly Val Tyr Gln Trp Leu Ser Leu Val Ile Leu Met Thr Gly
140 145 150
Val Ala Phe Val Gln Trp Pro Ser Asp Ser Gln Leu Asp Ser Lys
155 160 165
Glu Leu Ser Ala Gly Ser Gln Phe Val Gly Leu Met Ala Val Leu
170 175 180
Thr Ala Cys Phe Ser Ser Gly Phe Ala Gly Val Tyr Phe Glu Lys
185 190 195
Ile Leu Lys Glu Thr Lys Gln Ser Val Trp Ile Arg Asn Ile Gln
200 205 210
Leu Gly Phe Phe Gly Ser Ile Phe Gly Leu Met Gly Val Tyr Ile
215 220 225
Tyr Asp Gly Glu Leu Val Ser Lys Asn Gly Phe Phe Gln Gly Tyr
230 235 240
Asn Arg Leu Thr Trp Ile Val Val Val Leu Gln Ala Leu Gly Gly
245 250 255
Leu Val Ile Ala Ala Val Ile Lys Tyr Ala Asp Asn Ile Leu Lys
260 265 270
Gly Phe Ala Thr Ser Leu Ser Ile Ile Leu Ser Thr Leu Ile Ser
275 280 285
Tyr Phe Trp Leu Gln Asp Phe Val Pro Thr Ser Val Phe Phe Leu
290 295 300

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<400> 10
Met Glu Arg Glu Met Glu Gly Arg Pro Leu His Asn Glu Gly Trp
  1                      5                      10                      15
Ile Asp Arg Ser Arg Val Gln Gln Lys Asp Leu Pro Asn Lys Cys

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| | | | |
|---|-----|-----|-----|
| | 20 | 25 | 30 |
| Pro Gln Thr Leu Trp Ser Glu Gln Ala Phe Pro Pro Asn Pro Gly | | | |
| | 35 | 40 | 45 |
| Gln Val Gly Ile Val Gly Arg Thr Gly Ala Gly Lys Ser Ser Leu | | | |
| | 50 | 55 | 60 |
| Ala Ser Gly Leu Leu Arg Leu Pro Glu Ala Ala Glu Gly Gly Ile | | | |
| | 65 | 70 | 75 |
| Trp Ile Asp Gly Val Pro Ile Ala His Val Gly Leu His Thr Leu | | | |
| | 80 | 85 | 90 |
| Arg Ser Arg Ile Ser Ile Ile Pro Gln Asp Pro Ile Leu Phe Pro | | | |
| | 95 | 100 | 105 |
| Gly Ser Leu Arg Met Asn Leu Asp Leu Leu Gln Glu His Ser Asp | | | |
| | 110 | 115 | 120 |
| Glu Ala Ile Trp Ala Ala Leu Glu Thr Val Gln Leu Lys Ala Leu | | | |
| | 125 | 130 | 135 |
| Val Ala Ser Leu Pro Gly Gln Leu Gln Tyr Lys Cys Ala Asp Arg | | | |
| | 140 | 145 | 150 |
| Gly Glu Asp Leu Ser Val Gly Gln Lys Gln Leu Leu Cys Leu Ala | | | |
| | 155 | 160 | 165 |
| Arg Ala Leu Leu Arg Lys Thr Gln Ile Leu Ile Leu Asp Glu Ala | | | |
| | 170 | 175 | 180 |
| Thr Ala Ala Val Asp Pro Gly Thr Glu Leu Gln Met Gln Ala Met | | | |
| | 185 | 190 | 195 |
| Leu Gly Ser Trp Phe Ala Gln Cys Thr Val Leu Leu Ile Ala His | | | |
| | 200 | 205 | 210 |
| Arg Leu Arg Ser Val Met Asp Cys Ala Arg Val Leu Val Met Asp | | | |
| | 215 | 220 | 225 |
| Lys Gly Gln Val Ala Glu Ser Gly Ser Pro Ala Gln Leu Leu Ala | | | |
| | 230 | 235 | 240 |
| Gln Lys Gly Leu Phe Tyr Arg Leu Ala Gln Glu Ser Gly Leu Val | | | |
| | 245 | 250 | 255 |

<210> 11

<211> 462

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 1413743CD1

<400> 11

| | | |
|---|----|----|
| Met Ala Gln Val Ser Ile Asn Asn Asp Tyr Ser Glu Trp Asp Leu | | |
| 1 | 5 | 10 |
| Ser Thr Asp Ala Gly Glu Arg Ala Arg Leu Leu Gln Ser Pro Cys | | |
| | 20 | 25 |
| Val Asp Thr Ala Pro Lys Ser Glu Trp Glu Ala Ser Pro Gly Gly | | |
| | 35 | 40 |
| Leu Asp Arg Gly Thr Thr Ser Thr Leu Gly Ala Ile Phe Ile Val | | |
| | 50 | 55 |
| Val Asn Ala Cys Leu Gly Ala Gly Leu Leu Asn Phe Pro Ala Ala | | |
| | 65 | 70 |
| Phe Ser Thr Ala Gly Gly Val Ala Ala Gly Ile Ala Leu Gln Met | | |
| | 80 | 85 |

| | | | | | |
|---------------------|-----------------|-------------------------|-----|-----|-----|
| Gly Met Leu Val Phe | Ile Ile Ser Gly | Leu Val Ile Leu Ala Tyr | 95 | 100 | 105 |
| Cys Ser Gln Ala Ser | Asn Glu Arg Thr | Tyr Gln Glu Val Val Trp | 110 | 115 | 120 |
| Ala Val Cys Gly Lys | Leu Thr Gly Val | Leu Cys Glu Val Ala Ile | 125 | 130 | 135 |
| Ala Val Tyr Thr Phe | Gly Thr Cys Ile | Ala Phe Leu Ile Ile Ile | 140 | 145 | 150 |
| Gly Asp Gln Gln Asp | Lys Ile Ile Ala | Val Met Ala Lys Glu Pro | 155 | 160 | 165 |
| Glu Gly Ala Ser Gly | Pro Trp Tyr Thr | Asp Arg Lys Phe Thr Ile | 170 | 175 | 180 |
| Ser Leu Thr Ala Phe | Leu Phe Ile Leu | Pro Leu Ser Ile Pro Arg | 185 | 190 | 195 |
| Glu Ile Gly Phe Gln | Lys Tyr Ala Ser | Phe Leu Ser Val Val Gly | 200 | 205 | 210 |
| Thr Trp Tyr Val Thr | Ala Ile Val Ile | Ile Lys Tyr Ile Trp Pro | 215 | 220 | 225 |
| Asp Lys Glu Met Thr | Pro Gly Asn Ile | Leu Thr Arg Pro Ala Ser | 230 | 235 | 240 |
| Trp Met Ala Val Phe | Asn Ala Met Pro | Thr Ile Cys Phe Gly Phe | 245 | 250 | 255 |
| Gln Cys His Val Ser | Ser Val Pro Val | Phe Asn Ser Met Gln Gln | 260 | 265 | 270 |
| Pro Glu Val Lys Thr | Trp Gly Gly Val | Val Thr Ala Ala Met Val | 275 | 280 | 285 |
| Ile Ala Leu Ala Val | Tyr Met Gly Thr | Gly Ile Cys Gly Phe Leu | 290 | 295 | 300 |
| Thr Phe Gly Ala Ala | Val Asp Pro Asp | Val Leu Leu Ser Tyr Pro | 305 | 310 | 315 |
| Ser Glu Asp Met Ala | Val Ala Val Ala | Arg Ala Phe Ile Ile Leu | 320 | 325 | 330 |
| Ser Val Leu Thr Ser | Tyr Pro Ile Leu | His Phe Cys Gly Arg Ala | 335 | 340 | 345 |
| Val Val Glu Gly Leu | Trp Leu Arg Tyr | Gln Gly Val Pro Val Glu | 350 | 355 | 360 |
| Glu Asp Val Gly Arg | Glu Arg Arg Arg | Arg Val Leu Gln Thr Leu | 365 | 370 | 375 |
| Val Trp Phe Leu Leu | Thr Leu Leu Leu | Ala Leu Phe Ile Pro Asp | 380 | 385 | 390 |
| Ile Gly Lys Val Ile | Ser Val Ile Gly | Gly Leu Ala Ala Cys Phe | 395 | 400 | 405 |
| Ile Phe Val Phe Pro | Gly Leu Cys Leu | Ile Gln Ala Lys Leu Ser | 410 | 415 | 420 |
| Glu Met Glu Glu Val | Lys Pro Ala Ser | Trp Trp Val Leu Val Ser | 425 | 430 | 435 |
| Tyr Gly Val Leu Leu | Val Thr Leu Gly | Ala Phe Ile Phe Gly Gln | 440 | 445 | 450 |
| Thr Thr Ala Asn Ala | Ile Phe Val Asp | Leu Leu Ala | 455 | 460 | |

<210> 12

<211> 758

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 1733477CD1

<400> 12

| | | |
|---|-----|---------|
| Met Gly Leu Ala Asp Ala Ser Gly Pro Arg Asp Thr Gln Ala Leu | | |
| 1 | 5 | 10 15 |
| Leu Ser Ala Thr Gln Ala Met Asp Leu Arg Arg Arg Asp Tyr His | 20 | 25 30 |
| Met Glu Arg Pro Leu Leu Asn Gln Glu His Leu Glu Glu Leu Gly | 35 | 40 45 |
| Arg Trp Gly Ser Ala Pro Arg Thr His Gln Trp Arg Thr Trp Leu | 50 | 55 60 |
| Gln Cys Ser Arg Ala Arg Ala Tyr Ala Leu Leu Gln His Leu | 65 | 70 75 |
| Pro Val Leu Val Trp Leu Pro Arg Tyr Pro Val Arg Asp Trp Leu | 80 | 85 90 |
| Leu Gly Asp Leu Leu Ser Gly Leu Ser Val Ala Ile Met Gln Leu | 95 | 100 105 |
| Pro Gln Gly Leu Ala Tyr Ala Leu Leu Ala Gly Leu Pro Pro Val | 110 | 115 120 |
| Phe Gly Leu Tyr Ser Ser Phe Tyr Pro Val Phe Ile Tyr Phe Leu | 125 | 130 135 |
| Phe Gly Thr Ser Arg His Ile Ser Val Gly Thr Phe Ala Val Met | 140 | 145 150 |
| Ser Val Met Val Gly Gly Val Thr Glu Ser Leu Ala Pro Gln Ala | 155 | 160 165 |
| Leu Asn Asp Ser Met Ile Asn Glu Thr Ala Arg Asp Ala Ala Arg | 170 | 175 180 |
| Val Gln Val Ala Ser Thr Leu Ser Val Leu Val Gly Leu Phe Gln | 185 | 190 195 |
| Val Gly Leu Gly Leu Ile His Phe Gly Phe Val Val Thr Tyr Leu | 200 | 205 210 |
| Ser Glu Pro Leu Val Arg Gly Tyr Thr Thr Ala Ala Ala Val Gln | 215 | 220 225 |
| Val Phe Val Ser Gln Leu Lys Tyr Val Phe Gly Leu His Leu Ser | 230 | 235 240 |
| Ser His Ser Gly Pro Leu Ser Leu Ile Tyr Thr Val Leu Glu Val | 245 | 250 255 |
| Cys Trp Lys Leu Pro Gln Ser Lys Val Gly Thr Val Val Thr Ala | 260 | 265 270 |
| Ala Val Ala Gly Val Val Leu Val Val Val Lys Leu Leu Asn Asp | 275 | 280 285 |
| Lys Leu Gln Gln Gln Leu Pro Met Pro Ile Pro Gly Glu Leu Leu | 290 | 295 300 |
| Thr Leu Ile Gly Ala Thr Gly Ile Ser Tyr Gly Met Gly Leu Lys | 305 | 310 315 |
| His Arg Phe Glu Val Asp Val Val Gly Asn Ile Pro Ala Gly Leu | 320 | 325 330 |
| Val Pro Pro Val Ala Pro Asn Thr Gln Leu Phe Ser Lys Leu Val | 335 | 340 345 |
| Gly Ser Ala Phe Thr Ile Ala Val Val Gly Phe Ala Ile Ala Ile | 350 | 355 360 |

| | | | | | |
|---------------------|---------------------|-------------------------|-----|-----|-----|
| Ser Leu Gly Lys | Ile Phe Ala Leu Arg | His Gly Tyr Arg Val Asp | 365 | 370 | 375 |
| Ser Asn Gln Glu | Leu Val Ala Leu Gly | Leu Ser Asn Leu Ile Gly | 380 | 385 | 390 |
| Gly Ile Phe Gln Cys | Phe Pro Val Ser | Cys Ser Met Ser Arg Ser | 395 | 400 | 405 |
| Leu Val Gln Glu | Ser Thr Gly Gly Asn | Ser Gln Val Ala Gly Ala | 410 | 415 | 420 |
| Ile Ser Ser Leu | Phe Ile Leu Leu Ile | Ile Val Lys Leu Gly Glu | 425 | 430 | 435 |
| Leu Phe His Asp | Leu Pro Lys Ala Val | Leu Ala Ala Ile Ile Ile | 440 | 445 | 450 |
| Val Asn Leu Lys | Gly Met Leu Arg Gln | Leu Ser Asp Met Arg Ser | 455 | 460 | 465 |
| Leu Trp Lys Ala | Asn Arg Ala Asp Leu | Leu Ile Trp Leu Val Thr | 470 | 475 | 480 |
| Phe Thr Ala Thr | Ile Leu Leu Asn Leu | Asp Leu Gly Leu Val Val | 485 | 490 | 495 |
| Ala Val Ile Phe | Ser Leu Leu Leu Val | Val Val Arg Thr Gln Met | 500 | 505 | 510 |
| Pro His Tyr Ser | Val Leu Gly Gln Val | Pro Asp Thr Asp Ile Tyr | 515 | 520 | 525 |
| Arg Asp Val Ala | Glu Tyr Ser Glu Ala | Lys Glu Val Arg Gly Val | 530 | 535 | 540 |
| Lys Val Phe Arg | Ser Ser Ala Thr Val | Tyr Phe Ala Asn Ala Glu | 545 | 550 | 555 |
| Phe Tyr Ser Asp | Ala Leu Lys Gln Arg | Cys Gly Val Asp Val Asp | 560 | 565 | 570 |
| Phe Leu Ile Ser | Gln Lys Lys Lys Leu | Leu Lys Lys Gln Glu Gln | 575 | 580 | 585 |
| Leu Lys Leu Lys | Gln Leu Gln Lys Glu | Glu Lys Leu Arg Lys Gln | 590 | 595 | 600 |
| Ala Ala Ser Pro | Lys Gly Ala Ser Val | Ser Ile Asn Val Asn Thr | 605 | 610 | 615 |
| Ser Leu Glu Asp | Met Arg Ser Asn Asn | Val Glu Asp Cys Lys Met | 620 | 625 | 630 |
| Met Val Ser Ser | Gly Asp Lys Met Glu | Asp Ala Thr Ala Asn Gly | 635 | 640 | 645 |
| Gln Glu Asp Ser | Lys Ala Pro Asp Gly | Ser Thr Leu Lys Ala Leu | 650 | 655 | 660 |
| Gly Leu Pro Gln | Pro Asp Phe His Ser | Leu Ile Leu Asp Leu Gly | 665 | 670 | 675 |
| Ala Leu Ser Phe | Val Asp Thr Val Cys | Leu Lys Ser Leu Lys Asn | 680 | 685 | 690 |
| Ile Phe His Asp | Phe Arg Glu Ile Glu | Val Glu Val Tyr Met Ala | 695 | 700 | 705 |
| Ala Cys His Ser | Pro Val Val Ser Gln | Leu Glu Ala Gly His Phe | 710 | 715 | 720 |
| Phe Asp Ala Ser | Ile Thr Lys Lys His | Leu Phe Ala Ser Val His | 725 | 730 | 735 |
| Asp Ala Val Thr | Phe Ala Leu Gln His | Pro Arg Pro Val Pro Asp | 740 | 745 | 750 |
| Ser Pro Val Ser | Val Thr Arg Leu | | 755 | | |

| | | | | | | | | | | | | | | | |
|-------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|
| <400> | 13 | | | | | | | | | | | | | | |
| Met | Met | Gly | Pro | Gly | Leu | Ala | Phe | Gly | Leu | Gly | Ser | Leu | Met | Leu | |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |
| Arg | Leu | Tyr | Val | Asp | Ile | Asn | Gln | Met | Pro | Glu | Gly | Gly | Ile | Ser | |
| | | | | 20 | | | | | 25 | | | | | 30 | |
| Leu | Thr | Ile | Lys | Asp | Pro | Arg | Trp | Val | Gly | Ala | Trp | Trp | Leu | Gly | |
| | | | | 35 | | | | | 40 | | | | | 45 | |
| Phe | Leu | Ile | Ala | Ala | Gly | Ala | Val | Ala | Leu | Ala | Ala | Ile | Pro | Tyr | |
| | | | | 50 | | | | | 55 | | | | | 60 | |
| Phe | Phe | Phe | Pro | Lys | Glu | Met | Pro | Lys | Glu | Lys | Arg | Glu | Leu | Gln | |
| | | | | 65 | | | | | 70 | | | | | 75 | |
| Phe | Arg | Arg | Lys | Val | Leu | Ala | Val | Thr | Asp | Ser | Pro | Ala | Arg | Lys | |
| | | | | 80 | | | | | 85 | | | | | 90 | |
| Gly | Lys | Asp | Ser | Pro | Ser | Lys | Gln | Ser | Pro | Gly | Glu | Ser | Thr | Lys | |
| | | | | 95 | | | | | 100 | | | | | 105 | |
| Lys | Gln | Asp | Gly | Leu | Val | Gln | Ile | Ala | Pro | Asn | Leu | Thr | Val | Ile | |
| | | | | 110 | | | | | 115 | | | | | 120 | |
| Gln | Phe | Ile | Lys | Val | Phe | Pro | Arg | Val | Leu | Leu | Gln | Thr | Leu | Arg | |
| | | | | 125 | | | | | 130 | | | | | 135 | |
| His | Pro | Ile | Phe | Leu | Leu | Val | Val | Leu | Ser | Gln | Val | Cys | Leu | Ser | |
| | | | | 140 | | | | | 145 | | | | | 150 | |
| Ser | Met | Ala | Ala | Gly | Met | Ala | Thr | Phe | Leu | Pro | Lys | Phe | Leu | Glu | |
| | | | | 155 | | | | | 160 | | | | | 165 | |
| Arg | Gln | Phe | Ser | Ile | Thr | Ala | Ser | Tyr | Ala | Asn | Leu | Leu | Ile | Gly | |
| | | | | 170 | | | | | 175 | | | | | 180 | |
| Cys | Leu | Ser | Phe | Pro | Ser | Val | Ile | Val | Gly | Ile | Val | Val | Gly | Gly | |
| | | | | 185 | | | | | 190 | | | | | 195 | |
| Val | Leu | Val | Lys | Arg | Leu | His | Leu | Gly | Pro | Val | Gly | Cys | Gly | Ala | |
| | | | | 200 | | | | | 205 | | | | | 210 | |
| Leu | Cys | Leu | Leu | Gly | Met | Leu | Leu | Cys | Leu | Phe | Phe | Ser | Leu | Pro | |
| | | | | 215 | | | | | 220 | | | | | 225 | |
| Leu | Phe | Phe | Ile | Gly | Cys | Ser | Ser | His | Gln | Ile | Ala | Gly | Ile | Thr | |
| | | | | 230 | | | | | 235 | | | | | 240 | |
| His | Gln | Thr | Ser | Ala | His | Pro | Gly | Leu | Glu | Leu | Ser | Pro | Ser | Cys | |
| | | | | 245 | | | | | 250 | | | | | 255 | |
| Met | Glu | Ala | Cys | Ser | Cys | Pro | Leu | Asp | Gly | Phe | Asn | Pro | Val | Cys | |
| | | | | 260 | | | | | 265 | | | | | 270 | |
| Asp | Pro | Ser | Thr | Arg | Val | Glu | Tyr | Ile | Thr | Pro | Cys | His | Ala | Gly | |
| | | | | 275 | | | | | 280 | | | | | 285 | |
| Cys | Ser | Ser | Trp | Val | Val | Gln | Asp | Ala | Leu | Asp | Asn | Ser | Gln | Ser | |
| | | | | 290 | | | | | 295 | | | | | 300 | |
| Pro | Pro | Thr | Ser | His | Pro | His | Ala | Gly | His | Gln | His | Leu | Asn | Leu | |
| | | | | 305 | | | | | 310 | | | | | 315 | |
| Arg | Leu | Leu | Gln | Gly | Glu | Thr | Trp | Ala | Ala | Leu | Ala | Gly | Ala | Glu | |
| | | | | 320 | | | | | 325 | | | | | | |

335

<210> 14
 <211> 103
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte ID No: 2656554CD1

<400> 14
 Met Glu Arg Gln Ser Arg Val Met Ser Glu Lys Asp Glu Tyr Gln
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 Phe Gln His Gln Gly Ala Val Glu Leu Leu Val Phe Asn Phe Leu
 20 25 30
 Leu Ile Leu Thr Ile Leu Thr Ile Trp Leu Phe Lys Asn His Arg
 35 40 45
 Phe Arg Phe Leu His Glu Thr Gly Gly Ala Met Val Tyr Asp Lys
 50 55 60
 Pro Pro Lys Phe Ala Met Ser Arg Glu Gln Met Ser Gln Ser Cys
 65 70 75
 Ser His Thr Ala His Asn Ala Ser Leu Leu Thr Asp Ala Gly Pro
 80 85 90
 Leu Ser Cys Gly Glu Ser Arg Ala Ser Cys Leu Phe Leu
 95 100

<210> 15
 <211> 123
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte ID No: 2719228CD1

<400> 15
 Met Gln Gly Met Gly Leu Gly Leu Ser Ser Val Phe Ala Leu Cys
 1 5 10 15
 Leu Gly His Thr Ser Ser Phe Cys Glu Ser Val Val Phe Ala Ser
 20 25 30
 Ala Ser Ile Gly Leu Gln Thr Phe Asn His Ser Gly Ile Ser Val
 35 40 45
 Asn Ile Gln Asp Leu Ala Pro Ser Cys Ala Gly Phe Leu Phe Gly
 50 55 60
 Val Ala Asn Thr Ala Gly Ala Leu Ala Gly Val Val Gly Val Cys
 65 70 75
 Leu Gly Gly Tyr Leu Met Glu Thr Thr Gly Ser Trp Thr Cys Leu
 80 85 90
 Phe Asn Leu Val Ala Ile Ile Ser Asn Leu Gly Leu Cys Thr Phe
 95 100 105
 Leu Val Phe Gly Gln Ala Gln Arg Val Asp Leu Ser Ser Thr His
 110 115 120

Glu Asp Leu

<210> 16
 <211> 222
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte ID No: 3657824CD1

<400> 16
 Met Lys Gln Glu Ser Ala Ala Pro Asn Thr Pro Pro Thr Ser Gln
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 Ser Pro Thr Pro Ser Ala Gln Phe Pro Arg Asn Asp Gly Asp Pro
 20 25 30
 Gln Ala Leu Trp Ile Phe Gly Tyr Gly Ser Leu Val Trp Arg Pro
 35 40 45
 Asp Phe Ala Tyr Ser Asp Ser Arg Val Gly Phe Val Arg Gly Tyr
 50 55 60
 Ser Arg Arg Phe Trp Gln Gly Asp Thr Phe His Arg Gly Ser Asp
 65 70 75
 Lys Met Pro Gly Arg Val Val Thr Leu Leu Glu Asp His Glu Gly
 80 85 90
 Cys Thr Trp Gly Val Ala Tyr Gln Val Gln Gly Glu Gln Val Ser
 95 100 105
 Lys Ala Leu Lys Tyr Leu Asn Val Arg Glu Ala Val Leu Gly Gly
 110 115 120
 Tyr Asp Thr Lys Glu Val Thr Phe Tyr Pro Gln Asp Ala Pro Asp
 125 130 135
 Gln Pro Leu Lys Ala Leu Ala Tyr Val Ala Thr Pro Gln Asn Pro
 140 145 150
 Gly Tyr Leu Gly Pro Ala Pro Glu Glu Ala Ile Ala Thr Gln Ile
 155 160 165
 Leu Ala Cys Arg Gly Phe Ser Gly His Asn Leu Glu Tyr Leu Leu
 170 175 180
 Arg Leu Ala Asp Phe Met Gln Leu Cys Gly Pro Gln Ala Gln Asp
 185 190 195
 Glu His Leu Ala Ala Ile Val Asp Ala Val Gly Thr Met Leu Pro
 200 205 210
 Cys Phe Cys Pro Thr Glu Gln Ala Leu Ala Leu Val
 215 220

<210> 17
 <211> 111
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte ID No: 5378485CD1

<400> 17
 Met Leu Ser Ala Leu Pro Gly Trp Gly Pro Ala His Leu Gln Arg

| | | | |
|-----------------|-------------------------|-----------------|-----|
| 1 | 5 | 10 | 15 |
| Pro Leu Leu Gly | Pro Ala Ser Cys Leu Gly | Ile Leu Arg Pro | Ala |
| 20 | 25 | 30 | |
| Met Thr Ala His | Ser Phe Ala Leu Pro Val | Ile Ile Phe Thr | Thr |
| 35 | 40 | 45 | |
| Phe Trp Gly Leu | Val Gly Ile Ala Gly Pro | Trp Phe Val Pro | Lys |
| 50 | 55 | 60 | |
| Gly Pro Asn Arg | Gly Val Ile Ile Thr Met | Leu Val Ala Thr | Ala |
| 65 | 70 | 75 | |
| Val Cys Cys Tyr | Leu Phe Trp Leu Ile Ala | Ile Leu Ala Gln | Leu |
| 80 | 85 | 90 | |
| Asn Pro Leu Phe | Gly Pro Gln Leu Lys Asn | Glu Thr Ile Trp | Tyr |
| 95 | 100 | 105 | |
| Val Arg Phe Leu | Trp Glu | | |
| 110 | | | |

<210> 18

<211> 1303

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 961344CB1

<400> 18

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agctacctgc attgccaaaa gttcacatct cgtgtctaga acacaagata ttcataatttt 120
cagacaggta accagtcggg gagaggcaca tttggagctg aatgcatttc gaaggaagca 180
tgattgtgca ctagtcatat ctggggactc tctggagggt tgtctaaagt actacgagca 240
tgaatttgtg gagctggcct gccagtgcct tgcctgggtt tgctgccgct gctcaccac 300
ccagaaggcc cgcattgtga cactgctgca gcagcacaca gggagacgca cctgcgccat 360
cgggtgatga ggaaatgatg tcagcatgat tcaggcagca gactgtggga ttgggattga 420
gggaaaggag ggtaaacagg cctcgctggc ggccgacttc tccatcacgc agttccggca 480
cataggcagg ctgctcatgg tgcacgggcg gaacagctac aagaggctcg cggcactcgg 540
ccagttcgtc atgcacaggg gccttateat ctccaccatg caggctgtgt tttcctcagt 600
cttctacttc gcatccgtcc ctttgtatca gggcttctc atgggtgggt atgccaccat 660
atacaccatg tccccagtgt tctccttagt gctggaccag gacgtgaagc cagagatggc 720
gatgctctac ccggagctgt acaaggacct caccaaggga agatccttgt ccttcaaaac 780
cttcctcatc tgggttttaa taagtattta ccaaggcggc atcctcatgt atggggccct 840
ggtgctcttc gagtctgagt tcgtccacgt ggtggccatc tccttcaccg cactgatcct 900
gaccgagctg ctgatggtgg cgtgaccgt ccgcacgtgg cactggctga tgggtggggtg 960
cgagtctctc agcttaggct gctacgtgtc ctactcgtc tttctcaatg aatattttgg 1020
tataggcaga gtgtcttttg gagctttctt agatgttgcc tttatcacca ccgtgacctt 1080
cctgtggaaa gtgtcggcga tcaccgtggt cagctgcctc ccgctgtatg tcctcaagta 1140
cctgaggcgc aagctctctc ctcccagcta ctgcaagctg gcctcctaag gggctgtgca 1200
ccccacgcgc gctggcccca gcacctctg cccttcccag caccttgtgc ccttgccagt 1260
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<210> 19

<211> 3395

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 3128782CB1

<400> 19

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acaaagtggg gaagaaaggg aagaaggaca agaagatcaa aaaaacgttc tttgaagagc 180
tggcagtaga agataaacag gctggggaag aagagaaagt gctcaaggag aaggagcagc 240
agcagcagca acagcaacag cagcagcaa aaaaaaagcg agataccgga aaaggcaggc 300
ggaagaagga tgtggatgat gatggagaag agaaagagct catggagcgt cttaaagaagc 360
tctcagtgcc aaccagtgat gaggagatg aagtccccgc cccaaaaccg cgcgagggga 420
agaaaaccac ggggtggtat gtttttgcag ccttgattca ggatcagagt gaggaagagg 480
aggaggaaga aaaacatcct cctaagcctg ccaagccgga gaagaatcgg atcaataagg 540
ccgtatctga ggaacagcag cctgcactca agggcaaaaa gggaaaggaa gagaagtcaa 600
aagggaaggc taagcctcaa aataaattcg ctgctctgga caatgaagag gaggataaag 660
aagaagaaat tataaaggaa aaggagcctc ccaacaaggg gaaggagaag gccaaagaag 720
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<212> DNA

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<223> Incyte ID No: 2617942CB1

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<211> 1141

<212> DNA

<213> Homo sapiens

<220>

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 <213> Homo sapiens

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 <221> misc_feature
 <223> Incyte ID No: 4074113CB1

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 <212> DNA
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<210> 29

<211> 2580

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 1733477CB1

<400> 29

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<210> 30

<211> 1481

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 2641908CB1

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<210> 31

<211> 667

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 2656554CB1

<400> 31

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<210> 32

<211> 1635

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 2719228CB1

<400> 32

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<210> 33

<211> 1447

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 3657824CB1

<400> 33

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gccccgaaca ccccgccac ctgcagtc cctacgcgt ccgctcagtt cccccgaaac 180
gacggcgacc ctcaagcgt gtggatttcc gggtagggct ccctggtgtg gaggcccgac 240
ttgcctaca gcgacagccg tgtgggcttc gtgcgggt acagccgccc ttcttgccag 300
ggagacacct tccatcgggg cagcgacaag atgcctggcc gtgtggtgac gctccttgaa 360
gatcatgagg gctgcacttg gggcgtggca taccaagtgc aaggggagca ggtaagcaag 420
gcctgaagt acctgaatgt gcgagaggca gtgcttgggt gctacgatac caaggaggtc 480
accttctatc cccaagatgc tcctgaccaa ccactgaagg cattggccta tgtggccacc 540
ccacagaacc ctggttacct gggccctgcg cctgaagagg ccattgcccac gcagatcctg 600
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cagctctgtg ggctcaggc gcaggacgag cacctggcag ccctcgtgga cgctgtgggc 720
accatgttgc cctgctctg cccacccag caggctctgg cgctggtgtg aggggctgag 780
ccctgcggg gagtgctcat gtggacatca gggccagaca cccactccag tgcacaagac 840
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ctcagtcctt gcctgtctgc cagcctgcag ctctcctgct tgacactgac ttactacttg 960
aaactttatt tattgcacca tgttggtgtg gtgggcagggt ggagggcctg ccctggacac 1020

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agggggccctg ctgagcagtg gccccatcct ggaacttgac cagattcccc ccagtgtgtc 1080
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aggctggatg agggatagta gggcatgagg agaaggagcc ctgtaaggac tgaggccccg 1260
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<210> 34

<211> 657

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 5378485CB1

<400> 34

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ggttcgtgccc gaagggaccc aaccgcggag tgatcatcac catgctggtc gccaccgccc 240
tctgtctgta cctcttctgg ctcatcgcca tctggcgca gctgaacccc ctgttcgggc 300
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gtccgggaccc tccccacac aactatgtct ggtcaccagc tccctcctgc tggcaccag 480
agacccggac ccgcaggccc tgcctggctc ctggaagtct tcccagtctt cccagccagc 540
ccggggcccct ggggagccc gggcacagca gcggccgagg ggatgtcctg ctccaatact 600
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<210> 35

<211> 646

<212> PRT

<213> Mus musculus

<300>

<308> GenBank ID No: g2612939

<400> 35

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  20          25          30
Ala Phe Cys Val Tyr Val Gly Gly Gly Gly Trp Arg Phe Leu Arg
  35          40          45
Ile Val Cys Lys Thr Ala Arg Arg Asp Leu Phe Gly Leu Ser Val
  50          55          60
Leu Ile Arg Val Arg Leu Glu Leu Arg Arg His Arg Arg Ala Gly
  65          70          75
Asp Thr Ile Pro Cys Ile Phe Gln Ala Val Ala Arg Arg Gln Pro
  80          85          90
Glu Arg Leu Ala Leu Val Asp Ala Ser Ser Gly Ile Cys Trp Thr
  95          100         105

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36

| | | | |
|-----------------|---------------------|-------------------------|-----|
| | 515 | 520 | 525 |
| Ala Val Leu Ser | Arg Leu Leu Gly Gln | Thr Asp Val Ala Val Tyr | |
| | 530 | 535 | 540 |
| Gly Val Ala Val | Pro Gly Val Glu Gly | Lys Ala Gly Met Ala Ala | |
| | 545 | 550 | 555 |
| Ile Ala Asp Pro | His Ser Gln Leu Asp | Pro Asn Ser Met Tyr Gln | |
| | 560 | 565 | 570 |
| Glu Leu Gln Lys | Val Leu Ala Ser Tyr | Ala Arg Pro Ile Phe Leu | |
| | 575 | 580 | 585 |
| Arg Leu Leu Pro | Gln Val Asp Thr Thr | Gly Thr Phe Lys Ile Gln | |
| | 590 | 595 | 600 |
| Lys Thr Arg Leu | Gln Arg Glu Gly Phe | Asp Pro Arg Gln Thr Ser | |
| | 605 | 610 | 615 |
| Asp Arg Leu Phe | Phe Leu Asp Leu Lys | Gln Gly Arg Tyr Val Pro | |
| | 620 | 625 | 630 |
| Leu Asp Glu Arg | Val His Ala Arg Ile | Cys Ala Gly Asp Phe Ser | |
| | 635 | 640 | 645 |
| Leu | | | |

<210> 36

<211> 691

<212> PRT

<213> Schistosoma mansoni

<300>

<308> GenBank ID No: g425474

<400> 36

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| 20 25 30 | |
| Thr His Ile Lys Pro Leu Lys Cys Ser Ser Leu Arg Leu Thr | |
| 35 40 45 | |
| Val Gly Thr Gly Leu Phe Ile Ala Leu His Ser Lys Ile Ser Pro | |
| 50 55 60 | |
| Glu Ser Arg Ile Gln Thr Val Gln Cys Glu Val Asp Ser Tyr Gln | |
| 65 70 75 | |
| Thr Asp Gln Ile Thr Phe Ala Lys Ser Gly Gly Ile Pro Arg Tyr | |
| 80 85 90 | |
| Ile Gly Val Leu Ile Leu Pro Asp Cys Val Tyr Leu Phe Gly Ala | |
| 95 100 105 | |
| Ile Leu Gly Ala Phe Val Ala Ala Val Met Asn Val Tyr Ile Pro | |
| 110 115 120 | |
| Leu Tyr Leu Gly Asp Phe Val Ser Ser Leu Ser Arg Cys Val Val | |
| 125 130 135 | |
| Thr His Glu Gly Phe Val Ser Ala Val Tyr Val Pro Thr Leu Arg | |
| 140 145 150 | |
| Leu Cys Ser Ser Tyr Leu Leu Gln Ser Leu Ser Thr Phe Leu Tyr | |
| 155 160 165 | |
| Ile Gly Leu Leu Gly Ser Val Gly Glu Arg Met Ala Arg Arg Met | |
| 170 175 180 | |
| Arg Ile Gln Leu Phe Arg Lys Leu Val Tyr Gln Asp Val Ala Tyr | |
| 185 190 195 | |

| | | | |
|-----------------|-------------------------|-------------------------|-----|
| Phe Asp Val His | Ser Ser Gly Lys Leu Val | Glu Ile Ile Gly Ser | |
| | 200 | 205 | 210 |
| Asp Val Gln Asn | Phe Lys Ser Ser Phe | Lys Gln Cys Ile Ser Gln | |
| | 215 | 220 | 225 |
| Gly Leu Arg Asn | Gly Ile Gln Val Val | Gly Ser Val Phe Ala Leu | |
| | 230 | 235 | 240 |
| Leu Ser Ile Ser | Pro Thr Leu Thr Ala | Ala Leu Ile Gly Cys Leu | |
| | 245 | 250 | 255 |
| Pro Cys Val Phe | Leu Ile Gly Ser Leu | Met Gly Thr Glu Leu Arg | |
| | 260 | 265 | 270 |
| His Ile Ser Arg | Glu Val Gln Ser Gln | Asn Ser Leu Phe Ala Ser | |
| | 275 | 280 | 285 |
| Leu Ile Asp Glu | Ala Phe Ser His Ile | Arg Thr Val Lys Ser Leu | |
| | 290 | 295 | 300 |
| Ala Met Glu Asp | Phe Leu Ile Asn Lys | Ile Asn Tyr Asn Val Asp | |
| | 305 | 310 | 315 |
| Lys Ala Lys Met | Leu Ser Glu Lys Leu | Ser Phe Gly Ile Gly Ser | |
| | 320 | 325 | 330 |
| Phe Gln Gly Leu | Ser Asn Leu Thr Leu | Asn Gly Val Val Leu Gly | |
| | 335 | 340 | 345 |
| Val Leu Tyr Val | Gly Gly His Leu Met | Ser Arg Gly Glu Leu Asp | |
| | 350 | 355 | 360 |
| Ala Gly His Leu | Met Ser Phe Leu Ala | Thr Thr Gln Thr Leu Gln | |
| | 365 | 370 | 375 |
| Arg Ser Leu Thr | Gln Leu Ser Leu Leu | Tyr Gly Gln Val Val Arg | |
| | 380 | 385 | 390 |
| Gly Tyr Thr Ala | Leu Lys Arg Ile His | Asp Ile Leu Ala Leu Pro | |
| | 395 | 400 | 405 |
| Ser Gly Ile Gly | Ser Ile Pro Ser Ser | Ser Ser Ser Leu Val Val | |
| | 410 | 415 | 420 |
| Ser Lys Gln His | Val Asn Asn Ile Lys | Glu Leu Pro Ser Ser Ser | |
| | 425 | 430 | 435 |
| Ile Tyr Ser Ala | Pro Ser Ile Glu Phe | Ser Asp Val Lys Phe Ala | |
| | 440 | 445 | 450 |
| Tyr Pro Asn Arg | Pro Glu Thr Ile Val | Leu Asn Glu Leu Ser Met | |
| | 455 | 460 | 465 |
| Phe Leu Pro Gly | Gly Lys Val Ile Ala | Leu Val Gly Gln Ser Gly | |
| | 470 | 475 | 480 |
| Ala Gly Lys Ser | Thr Val Val Ser Leu | Leu Glu Arg Phe Tyr Asp | |
| | 485 | 490 | 495 |
| Pro Ile Ser Gly | Glu Ile Leu Leu Asn | Gly Asp Lys Leu Thr Asn | |
| | 500 | 505 | 510 |
| Phe Asn Val Asn | Tyr Leu Arg Ser Lys | Leu Ile Gly Tyr Ile Ser | |
| | 515 | 520 | 525 |
| Gln Glu Pro Gln | Ile Phe Asn Ala Ser | Ile Arg Glu Asn Ile Arg | |
| | 530 | 535 | 540 |
| Phe Gly Arg Phe | Asp Ala Thr Asp Glu | Glu Val Glu Glu Ala Ala | |
| | 545 | 550 | 555 |
| Lys Leu Ala Tyr | Ala His Asp Phe Ile | Ser Asn Asp Leu Pro Tyr | |
| | 560 | 565 | 570 |
| Gly Tyr Asp Thr | Leu Val Gly Gln Gly | Thr Gly Thr Ile Ala Gly | |
| | 575 | 580 | 585 |
| Leu Ser Gly Gly | Gln Arg Gln Arg Ile | Ala Ile Ala Arg Ile Leu | |
| | 590 | 595 | 600 |
| Leu Lys Asn Ala | Pro Ile Leu Leu Met | Asp Glu Ala Thr Ser Ala | |

| <400> 37 | | | | | | | | | | | | | | |
|----------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Thr | Val | Ala | Ser | Thr | Ala | Ala | Pro | Ser | Tyr | Thr | Thr | Ser | Asp |
| 1 | | | | 5 | | | | | 10 | | | | | 15 |
| Thr | Asn | Arg | Val | Ile | Ser | Thr | Phe | Ser | Val | Val | Asp | Tyr | Val | Val |
| | | | | 20 | | | | | 25 | | | | | 30 |
| Phe | Gly | Leu | Leu | Leu | Val | Leu | Ser | Leu | Val | Ile | Gly | Leu | Tyr | His |
| | | | | 35 | | | | | 40 | | | | | 45 |
| Ala | Cys | Arg | Gly | Trp | Gly | Arg | His | Thr | Val | Gly | Glu | Leu | Leu | Met |
| | | | | 50 | | | | | 55 | | | | | 60 |
| Ala | Asp | Arg | Lys | Met | Gly | Cys | Leu | Pro | Val | Ala | Leu | Ser | Leu | Leu |
| | | | | 65 | | | | | 70 | | | | | 75 |
| Ala | Thr | Phe | Gln | Ser | Ala | Val | Ala | Ile | Leu | Gly | Gly | Pro | Ala | Glu |
| | | | | 80 | | | | | 85 | | | | | 90 |
| Ile | Tyr | Arg | Phe | Gly | Thr | Gln | Tyr | Trp | Phe | Leu | Gly | Cys | Ser | Tyr |
| | | | | 95 | | | | | 100 | | | | | 105 |
| Phe | Leu | Gly | Leu | Leu | Ile | Pro | Ala | His | Ile | Phe | Ile | Pro | Val | Phe |
| | | | | 110 | | | | | 115 | | | | | 120 |
| Tyr | Arg | Leu | His | Leu | Thr | Ser | Ala | Tyr | Glu | Tyr | Leu | Glu | Leu | Arg |
| | | | | 125 | | | | | 130 | | | | | 135 |
| Phe | Asn | Lys | Ala | Val | Arg | Ile | Cys | Gly | Thr | Val | Thr | Phe | Ile | Phe |
| | | | | 140 | | | | | 145 | | | | | 150 |
| Gln | Met | Val | Val | Tyr | Met | Gly | Val | Ala | Leu | Tyr | Ala | Pro | Ser | Leu |
| | | | | 155 | | | | | 160 | | | | | 165 |
| Ala | Leu | Asn | Ala | Val | Thr | Gly | Phe | Asp | Leu | Trp | Leu | Ser | Val | Leu |
| | | | | 170 | | | | | 175 | | | | | 180 |
| Ala | Leu | Gly | Ile | Val | Cys | Asn | Ile | Tyr | Thr | Ala | Leu | Gly | Gly | Leu |
| | | | | 185 | | | | | 190 | | | | | 195 |
| Lys | Ala | Val | Ile | Trp | Thr | Asp | Val | Phe | Gln | Thr | Leu | Ile | Met | Phe |
| | | | | 200 | | | | | 205 | | | | | 210 |
| Leu | Gly | Gln | Leu | Val | Val | Ile | Ile | Val | Gly | Ala | Ala | Lys | Val | Gly |
| | | | | 215 | | | | | 220 | | | | | 225 |
| Gly | Leu | Gly | His | Val | Trp | Ala | Val | Ala | Ser | Gln | His | Gly | Leu | Ile |
| | | | | 230 | | | | | 235 | | | | | 240 |

| | | | |
|-----------------|---------------------|---------------------|-----|
| Ser Gly Ile Glu | Leu Asp Pro Asp Pro | Phe Val Arg His Thr | Phe |
| | 245 | 250 | 255 |
| Trp Thr Leu Ala | Phe Gly Gly Val Phe | Met Met Leu Ser Leu | Tyr |
| | 260 | 265 | 270 |
| Gly Val Asn Gln | Ala Gln Val Gln Arg | Tyr Leu Ser Ser His | Ser |
| | 275 | 280 | 285 |
| Glu Lys Ala Ala | Val Leu Ser Cys Tyr | Ala Val Phe Pro Cys | Gln |
| | 290 | 295 | 300 |
| Gln Val Ala Leu | Cys Met Ser Cys Leu | Ile Gly Leu Val Met | Phe |
| | 305 | 310 | 315 |
| Ala Tyr Tyr Lys | Lys Tyr Ser Met Ser | Pro Gln Gln Glu Gln | Ala |
| | 320 | 325 | 330 |
| Ala Pro Asp Gln | Leu Val Leu Tyr Phe | Val Met Asp Leu Leu | Lys |
| | 335 | 340 | 345 |
| Asp Met Pro Gly | Leu Pro Gly Leu Phe | Val Ala Cys Leu Phe | Ser |
| | 350 | 355 | 360 |
| Gly Ser Leu Ser | Thr Ile Ser Ser Ala | Phe Asn Ser Leu Ala | Thr |
| | 365 | 370 | 375 |
| Val Thr Met Glu | Asp Leu Ile Gln Pro | Trp Phe Pro Gln Leu | Thr |
| | 380 | 385 | 390 |
| Glu Thr Arg Ala | Ile Met Leu Ser Arg | Ser Leu Ala Phe Ala | Tyr |
| | 395 | 400 | 405 |
| Gly Leu Val Cys | Leu Gly Met Ala Tyr | Val Ser Ser His Leu | Gly |
| | 410 | 415 | 420 |
| Ser Val Leu Gln | Ala Ala Leu Ser Ile | Phe Gly Met Val Gly | Gly |
| | 425 | 430 | 435 |
| Pro Leu Leu Gly | Leu Phe Cys Leu Gly | Met Phe Phe Pro Cys | Ala |
| | 440 | 445 | 450 |
| Asn Pro Leu Gly | Ala Ile Val Gly Leu | Leu Thr Gly Leu Thr | Met |
| | 455 | 460 | 465 |
| Ala Phe Trp Ile | Gly Ile Gly Ser Ile | Val Ser Arg Met Ser | Ser |
| | 470 | 475 | 480 |
| Ala Ala Ala Ser | Pro Pro Leu Asn Gly | Ser Ser Ser Phe Leu | Pro |
| | 485 | 490 | 495 |
| Ser Asn Leu Thr | Val Ala Thr Val Thr | Thr Leu Met Pro Ser | Thr |
| | 500 | 505 | 510 |
| Leu Ser Lys Pro | Thr Gly Leu Gln Gln | Phe Tyr Ser Leu Ser | Tyr |
| | 515 | 520 | 525 |
| Leu Trp Tyr Ser | Ala His Asn Ser Thr | Thr Val Ile Ala Val | Gly |
| | 530 | 535 | 540 |
| Leu Ile Val Ser | Leu Leu Thr Gly Gly | Met Arg Gly Arg Ser | Leu |
| | 545 | 550 | 555 |
| Asn Pro Gly Thr | Ile Tyr Pro Val Leu | Pro Lys Leu Leu Ala | Leu |
| | 560 | 565 | 570 |
| Leu Pro Leu Ser | Cys Gln Lys Arg Leu | Cys Trp Arg Ser His | Asn |
| | 575 | 580 | 585 |
| Gln Asp Ile Pro | Val Val Thr Asn Leu | Phe Pro Glu Lys Met | Gly |
| | 590 | 595 | 600 |
| Asn Gly Ala Leu | Gln Asp Ser Arg Asp | Lys Glu Arg Met Ala | Glu |
| | 605 | 610 | 615 |
| Asp Gly Leu Val | His Gln Pro Cys Ser | Pro Thr Tyr Ile Val | Gln |
| | 620 | 625 | 630 |
| Glu Thr Ser Leu | | | |

<210> 38
 <211> 507
 <212> PRT
 <213> Homo sapiens

<300>

<308> GenBank ID No: g3639058

<400> 38

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|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|----|
| Met | Ala | Gly | Ala | Gly | Pro | Lys | Arg | Arg | Ala | Leu | Ala | Ala | Pro | Ala | 1 | 5 | 10 | 15 |
| Ala | Glu | Glu | Lys | Glu | Glu | Ala | Arg | Glu | Lys | Met | Leu | Ala | Ala | Lys | 20 | 25 | 30 | |
| Ser | Ala | Asp | Gly | Ser | Ala | Pro | Ala | Gly | Glu | Gly | Glu | Gly | Val | Thr | 35 | 40 | 45 | |
| Leu | Gln | Arg | Asn | Ile | Thr | Leu | Leu | Asn | Gly | Val | Ala | Ile | Ile | Val | 50 | 55 | 60 | |
| Gly | Thr | Ile | Ile | Gly | Ser | Gly | Ile | Phe | Val | Thr | Pro | Thr | Gly | Val | 65 | 70 | 75 | |
| Leu | Lys | Glu | Ala | Gly | Ser | Pro | Gly | Leu | Ala | Leu | Val | Val | Trp | Ala | 80 | 85 | 90 | |
| Ala | Cys | Gly | Val | Phe | Ser | Ile | Val | Gly | Ala | Leu | Cys | Tyr | Ala | Glu | 95 | 100 | 105 | |
| Leu | Gly | Thr | Thr | Ile | Ser | Lys | Ser | Gly | Gly | Asp | Tyr | Ala | Tyr | Met | 110 | 115 | 120 | |
| Leu | Glu | Val | Tyr | Gly | Ser | Leu | Pro | Ala | Phe | Leu | Lys | Leu | Trp | Ile | 125 | 130 | 135 | |
| Glu | Leu | Leu | Ile | Ile | Arg | Pro | Ser | Ser | Gln | Tyr | Ile | Val | Ala | Leu | 140 | 145 | 150 | |
| Val | Phe | Ala | Thr | Tyr | Leu | Leu | Lys | Pro | Leu | Phe | Pro | Thr | Cys | Pro | 155 | 160 | 165 | |
| Val | Pro | Glu | Glu | Ala | Ala | Lys | Leu | Val | Ala | Cys | Leu | Cys | Val | Leu | 170 | 175 | 180 | |
| Leu | Leu | Thr | Ala | Val | Asn | Cys | Tyr | Ser | Val | Lys | Ala | Ala | Thr | Arg | 185 | 190 | 195 | |
| Val | Gln | Asp | Ala | Phe | Ala | Ala | Ala | Lys | Leu | Leu | Ala | Leu | Ala | Leu | 200 | 205 | 210 | |
| Ile | Ile | Leu | Leu | Gly | Phe | Val | Gln | Ile | Gly | Lys | Gly | Asp | Val | Ser | 215 | 220 | 225 | |
| Asn | Leu | Asp | Pro | Lys | Phe | Ser | Phe | Glu | Gly | Thr | Lys | Leu | Asp | Val | 230 | 235 | 240 | |
| Gly | Asn | Ile | Val | Leu | Ala | Leu | Tyr | Ser | Gly | Leu | Phe | Ala | Tyr | Gly | 245 | 250 | 255 | |
| Gly | Trp | Asn | Tyr | Leu | Asn | Phe | Val | Thr | Glu | Glu | Met | Ile | Asn | Pro | 260 | 265 | 270 | |
| Tyr | Arg | Asn | Leu | Pro | Leu | Ala | Ile | Ile | Ile | Ser | Leu | Pro | Ile | Val | 275 | 280 | 285 | |
| Thr | Leu | Val | Tyr | Val | Leu | Thr | Asn | Leu | Ala | Tyr | Phe | Thr | Thr | Leu | 290 | 295 | 300 | |
| Ser | Thr | Glu | Gln | Met | Leu | Ser | Ser | Glu | Ala | Val | Ala | Val | Asp | Phe | 305 | 310 | 315 | |
| Gly | Asn | Tyr | His | Leu | Gly | Val | Met | Ser | Trp | Ile | Ile | Pro | Val | Phe | 320 | 325 | 330 | |
| Val | Gly | Leu | Ser | Cys | Phe | Gly | Ser | Val | Asn | Gly | Ser | Leu | Phe | Thr | | | | |

| | | | | | |
|-----------------|---|-----|-----|--|-----|
| | 335 | | 340 | | 345 |
| Ser Ser Arg Leu | Phe Phe Val Gly Ser Arg Glu Gly His Leu | Pro | | | |
| | 350 | | 355 | | 360 |
| Ser Ile Leu Ser | Met Ile His Pro Gln Leu Leu Thr Pro Val | Pro | | | |
| | 365 | | 370 | | 375 |
| Ser Leu Val Phe | Thr Cys Val Met Thr Leu Leu Tyr Ala Phe | Ser | | | |
| | 380 | | 385 | | 390 |
| Lys Asp Ile Phe | Ser Val Ile Asn Phe Phe Ser Phe Phe Asn | Trp | | | |
| | 395 | | 400 | | 405 |
| Leu Cys Val Ala | Leu Ala Ile Ile Gly Met Ile Trp Leu Arg | His | | | |
| | 410 | | 415 | | 420 |
| Arg Lys Pro Glu | Leu Glu Arg Pro Ile Lys Val Asn Leu Ala | Leu | | | |
| | 425 | | 430 | | 435 |
| Pro Val Phe Phe | Ile Leu Ala Cys Leu Phe Leu Ile Ala Val | Ser | | | |
| | 440 | | 445 | | 450 |
| Phe Trp Lys Thr | Pro Val Glu Cys Gly Ile Gly Phe Thr Ile | Ile | | | |
| | 455 | | 460 | | 465 |
| Leu Ser Gly Leu | Pro Val Tyr Phe Phe Gly Val Trp Trp Lys | Asn | | | |
| | 470 | | 475 | | 480 |
| Lys Pro Lys Trp | Leu Leu Gln Gly Ile Phe Ser Thr Thr Val | Leu | | | |
| | 485 | | 490 | | 495 |
| Cys Gln Lys Leu | Met Gln Val Val Pro Gln Glu Thr | | | | |
| | 500 | | 505 | | |

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<211> 504

<212> PRT

<213> Homo sapiens

<300>

<308> GenBank ID No: g1840045

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| Gly Lys His Ser | Glu Gly Leu Leu Pro Val Ile Thr Pro Met | Ala |
| | 20 | 25 30 |
| Gly Asn Gln Arg | Val Glu Asp Pro Ala Arg Ser Cys Met Glu | Gly |
| | 35 | 40 45 |
| Lys Ser Phe Leu | Gln Lys Ser Pro Ser Lys Glu Pro His Phe | Thr |
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| | | | | | | | | | | | | | | |
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 260 265 270
 Asn Val Pro Val Thr Leu Ser Glu Glu Asn Arg Ser Glu Gly Lys
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| Val Phe Tyr Val | Leu Val Asn Ser Ser | Gln Thr Leu His Asn | Lys |
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| Thr Leu Leu Gln | Val Val Gly Val Val | Ser Val Ala Val Ala | Val |
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| Leu Ala Leu Ser | Tyr Ala Leu Thr Leu | Met Gly Met Phe Gln | Trp |
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| Cys Val Arg Gln | Ser Ala Glu Val Glu | Asn Met Met Ile Ser | Val |
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| Glu Arg Val Ile | Glu Tyr Thr Asp Leu | Glu Lys Glu Ala Pro | Trp |
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| Glu Tyr Gln Lys | Arg Pro Pro Pro Ala | Trp Pro His Glu Gly | Val |
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| Val Gly Ile Val | Gly Arg Thr Gly Ala | Gly Lys Ser Ser Leu | Ile |
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| Ser Ala Leu Phe | Arg Leu Ser Glu Pro | Glu Gly Lys Ile Trp | Ile |
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| Asp Lys Ile Leu | Thr Thr Glu Ile Gly | Leu His Asp Leu Arg | Lys |
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| Lys Met Ser Ile | Ile Pro Gln Glu Pro | Val Leu Phe Thr Gly | Thr |
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| Leu Trp Asn Ala Leu Gln Glu Val Gln Leu Lys Glu Thr Ile Glu | 740 | 745 | 750 |
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| Asn Thr Ile Ile Asp Ser Asp Lys Ile Met Val Leu Asp Ser Gly | 830 | 835 | 840 |
| Arg Leu Lys Glu Tyr Asp Glu Pro Tyr Val Leu Leu Gln Asn Lys | 845 | 850 | 855 |
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| Pro Glu Leu Pro Leu Ala Val Gln Gly Val Ser Phe Lys Ile His | 230 | 235 | 240 |
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| His Thr Leu Arg Ser Arg Ile Ser Ile Ile Pro Gln Asp Pro Ile | 290 | 295 | 300 |
| Leu Phe Pro Gly Ser Leu Arg Met Asn Leu Asp Leu Leu Gln Glu | 305 | 310 | 315 |
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| Gly Leu Val | | | |

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
11 May 2000 (11.05.2000)

PCT

(10) International Publication Number
WO 00/26245 A3

(51) International Patent Classification⁷: C12N 15/12,
C07K 14/47, 16/18, A61K 38/17, C12Q 1/68, C12N 1/21

(21) International Application Number: PCT/US99/26048

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(25) Filing Language: English

(26) Publication Language: English

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60/172,252 24 November 1998 (24.11.1998) US
60/172,214 22 December 1998 (22.12.1998) US
60/121,896 26 February 1999 (26.02.1999) US

(63) Related by continuation (CON) or continuation-in-part (CIP) to earlier applications:

US 60/172,255 (CIP)
Filed on 4 November 1998 (04.11.1998)
US 60/172,252 (CIP)
Filed on 24 November 1998 (24.11.1998)
US 60/172,214 (CIP)
Filed on 22 December 1998 (22.12.1998)
US 60/121,896 (CIP)
Filed on 26 February 1999 (26.02.1999)

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(72) Inventors; and

(75) Inventors/Applicants (for US only): HILLMAN, Jennifer, L. [US/US]; 230 Monroe Drive, #12, Mountain View, CA 94040 (US). YUE, Henry [US/US]; 826 Lois Avenue, Sunnyvale, CA 94087 (US). TANG, Y., Tom [CN/US];

4230 Ranwick Court, San Jose, CA 95118 (US). LAL, Preeti [IN/US]; 2382 Lass Drive, Santa Clara, CA 95054 (US). CORLEY, Neil, C. [US/US]; 1240 Dale Avenue, #30, Mountain View, CA 94040 (US). GUEGLER, Karl, J. [CH/US]; 1048 Oakland Avenue, Menlo Park, CA 94025 (US). BAUGHN, Mariah, R. [US/US]; 14244 Santiago Road, San Leandro, CA 94577 (US). AZIMZAI, Yalda [US/US]; 2045 Rock Springs Drive, Hayward, CA 94545 (US). LU, Dyung, Aina, M. [US/US]; 55 Park Belmont Place, San Jose, CA 95136 (US).

(74) Agents: BILLINGS, Lucy, J. et al.; Incyte Pharmaceuticals, Inc., 3174 Porter Drive, Palo Alto, CA 94304 (US).

(81) Designated States (national): AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— With international search report.

(88) Date of publication of the international search report:
19 April 2001

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 00/26245 A3

(54) Title: HUMAN MEMBRANE TRANSPORT PROTEINS

(57) Abstract: The invention provides human membrane transport proteins (MTRP) and polynucleotides which identify and encode MTRP. The invention also provides expression vectors, host cells, antibodies, agonists, and antagonists. The invention also provides methods for diagnosing, treating, or preventing disorders associated with expression of MTRP.

INTERNATIONAL SEARCH REPORT

 Internal Application No
 PCT/JJ 99/26048

 A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 C12N15/12 C07K14/47 C07K16/18 A61K38/17 C12Q1/68
 C12N1/21

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

 Minimum documentation searched (classification system followed by classification symbols)
 IPC 7 C07K C12N A61K C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| X | DATABASE GENEMBL [Online] 20 February 1998 (1998-02-20) HALLECK M.S. ET AL: "Homo sapiens putative ATPase mRNA, partial cds." XP002132693 Accession No. U78978 | 1-16, 19, 20 |
| A | - & HALLECK, M.S. ET AL.: "Multiple members of a third subfamily of P-type ATPases identified by genomic sequences and ESTs." GENOME RESEARCH, vol. 8, no. 4, April 1998 (1998-04), pages 354-361, XP002132690 figure 2B page 357 --- -/- | |

☒ Further documents are listed in the continuation of box C.☐ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "Z" document member of the same patent family

Date of the actual completion of the international search

15 March 2000

Date of mailing of the international search report

20. JUNI. 2000

Name and mailing address of the ISA

 European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax: (+31-70) 340-3016

Authorized officer

ALCONADA RODRIG., A

INTERNATIONAL SEARCH REPORT

Internat Application No
PCT/US 99/26048

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
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| 3 | X DATABASE GENEMBL [Online] 27 May 1998 (1998-05-27) STANCHI, F.: "Homo sapiens mRNA for putative ATPase, partial" XP002132694 Accession AJ006268 | 1-16, 19, 20 |
| 1 | A ALLIKMETS R ET AL: "Characterization of the human ABC superfamily: isolation and mapping of 21 new genes using the expressed sequence tags database." HUMAN MOLECULAR GENETICS, (1996 OCT) 5 (10) 1649-55., XP002132691 figures 2,3; table 1 | |
| 1 | A MASTROBERARDINO L ET AL: "Amino-acid transport by heterodimers of 4F2hc/CD98 and members of a permease family." NATURE, (1998 SEP 17) 395 (6699) 288-91., XP002132692 the whole document | |
| 1 | A SARDET C ET AL: "Molecular cloning, primary structure, and expression of the human growth factor-activatable Na ⁺ /H ⁺ antiporter." CELL, (1989 JAN 27) 56 (2) 271-80., XP000876824 the whole document | |
| 3 | | |

INTERNATIONAL SEARCH REPORT

Int. onal application No.
PCT/US 99/26048

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 19 and 20 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 17, 18
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-16, 19-20 (partially)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 1-16,19-20 (partially)

Human polypeptide comprising the amino acid sequence of SEQ ID NO:1 or any variant having at least 90% amino acid identity with said sequence, the polynucleotide sequence encoding said polypeptide (SEQ ID NO:18) and any variant having at least 90% identity with said polynucleotide sequence; a polynucleotide that hybridizes with said polynucleotide; methods for detection of the polynucleotide; expression vectors and hosts for the recombinant expression of said polypeptide; method for the production of said polypeptide; antibodies against said polypeptide, agonists, antagonists, pharmaceutical compositions containing said polypeptide and uses thereof for the treatment or prevention of a disorder.

2. Claims: 1-16,19-20 (partially)

As subject 1, but comprising the polypeptide sequence of SEQ ID NO:2 and the polynucleotide sequence of SEQ ID NO:19.

3. Claims: 1-16,19-20 (partially)

As subject 1, but comprising the polypeptide sequence of SEQ ID NO:3 and the polynucleotide sequence of SEQ ID NO:20.

4. Claims: 1-16,19-20 (partially)

As subject 1, but comprising the polypeptide sequence of SEQ ID NO:4 and the polynucleotide sequence of SEQ ID NO:21.

5. Claims: 1-16,19-20 (partially)

As subject 1, but comprising the polypeptide sequence of SEQ ID NO:5 and the polynucleotide sequence of SEQ ID NO:22.

6. Claims: 1-16,19-20 (partially)

As subject 1, but comprising the polypeptide sequence of SEQ ID NO:6 and the polynucleotide sequence of SEQ ID NO:23.

7. Claims: 1-16,19-20 (partially)

As subject 1, but comprising the polypeptide sequences of SEQ ID NO:7 and 11 and the respective polynucleotide sequences of SEQ ID NO:24 and 28.

8. Claims: 1-16,19-20 (partially)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

As subject 1, but comprising the polypeptide sequence of SEQ ID NO:8 and the polynucleotide sequence of SEQ ID NO:25.

9. Claims: 1-16,19-20 (partially)

As subject 1, but comprising the polypeptide sequence of SEQ ID NO:9 and the polynucleotide sequence of SEQ ID NO:26.

10. Claims: 1-16,19-20 (partially)

As subject 1, but comprising the polypeptide sequence of SEQ ID NO:10 and the polynucleotide sequence of SEQ ID NO:27.

11. Claims: 1-16,19-20 (partially)

As subject 1, but comprising the polypeptide sequence of SEQ ID NO:12 and the polynucleotide sequence of SEQ ID NO:29.

12. Claims: 1-16,19-20 (partially)

As subject 1, but comprising the polypeptide sequence of SEQ ID NO:13 and the polynucleotide sequence of SEQ ID NO:30.

13. Claims: 1-16,19-20 (partially)

As subject 1, but comprising the polypeptide sequence of SEQ ID NO:14 and the polynucleotide sequence of SEQ ID NO:31.

14. Claims: 1-16,19-20 (partially)

As subject 1, but comprising the polypeptide sequence of SEQ ID NO:15 and the polynucleotide sequence of SEQ ID NO:32.

15. Claims: 1-16,19-20 (partially)

As subject 1, but comprising the polypeptide sequence of SEQ ID NO:16 and the polynucleotide sequence of SEQ ID NO:33.

16. Claims: 1-16,19-20 (partially)

As subject 1, but comprising the polypeptide sequence of SEQ ID NO:17 and the polynucleotide sequence of SEQ ID NO:34.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 17,18

Present claims 17 and 18 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is not to be found, however, for any of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has not been carried out for those claims which do not appear to be supported and disclosed, namely those parts relating to the agonists and antagonists of the polypeptides of the invention.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.